CASE REPORT

Anti-Neutrophil Cytoplasmic Antibody-associated Vasculitis (AAV) Restricted to the Limbs: A Case Report

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Abstract:
A previously healthy 58-year-old man was admitted for muscle pain and weakness (manual muscle testing [MMT] of 4/4 for upper and lower limbs). We detected elevated levels of inflammatory makers and PR3-anti-neutrophil cytoplasmic antibody (ANCA). Subsequently, the muscle weakness rapidly progressed to an MMT of 2 for all limbs. Magnetic resonance imaging indicated muscle edema, and the CK level increased to 29,998 U/L. mPSL and cyclophosphamide pulse therapy improved the patient symptoms. MMT recovered to 4 for all limbs. A muscle biopsy showed degenerated muscle fibers surrounded by neutrophil-predominant infiltration. In addition, lamina elastic breakdown and fibrinoid necrosis of arterioles were observed. A final diagnosis of microscopic polyangiitis (MPA) limited to the muscles was made.

Key words: ANCA-associated vasculitis, organ limited vasculitis, PR3-ANCA

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Introduction

Systemic vasculitis usually affects multiple organ systems. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a common cause of systemic vasculitis (1). The disease frequently affects the lungs, kidneys, and nervous and cutaneous systems. In contrast to systemic vasculitis, vasculitis limited to single organs has also been identified (2). For example, renal- and pulmonary-limited types are considered mild forms of AAV (2, 3). In addition to these major target organs, other organs can occasionally be affected. For example, otitis media with AAV (OMAAV) is considered a part of limited organ-type vasculitis (4). Hepatic aneurysm is another rare presentation of AAV (5-8), and retinal, breast, and urogenital structures can also become target organs on occasion (9). In addition, muscles can also become a target organ of vasculitis (10-12). Previous reports have shown that the lower limbs are primarily affected in vasculitis.

We herein report an unusual case of vasculitis that affects all limbs.

Case Report

A 58-year-old Japanese man was referred to our hospital for muscle pain and weakness. Two weeks before admission, the patient noticed left-knee pain. A prior physician diagnosed the patient as gout arthritis, given that the patient had a history of several previous gout attacks. Non-steroidal anti-inflammatory drugs, vitamin B12, and allopurinol were administered. One week before admission, the patient experienced worsening pain in his limbs and was unable to stand up alone. The patient was then brought to the hospital. He had been healthy before this episode, except for having gout arthritis. He took no medications except for a prior prescription from his physician. He was a current smoker (40 packs over 40 years) and drank 1-2 L of beer daily. He had no history of traveling abroad or contact with animals during the last year.

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The patient’s height was 163 cm, and he weighed 61.9 kg. Involuntary weight loss was not reported. His blood pressure was 162/102 mmHg, heart rate was a regular 109 beats per minute, and body temperature was 37.5 °C. He reported not feeling cold. His respiratory rate was 16 breaths per minute. SpO₂ was 97% in room air. A physical examination showed no remarkable findings expect for muscle weakness and tenderness. Manual muscle testing (MMT) was 4/5 for both his upper and lower limbs. The detailed MMT results were as follows: MMT (R/L) trapezius 4/4, deltoid 4/4, biceps 4/4, triceps 4/4, brachioradialis 4/4, iliopsoas 4/4, quadriceps 4/4, hamstrings 4/4, anterior tibialis 4/4, and gastrocnemius 4/4. The extent of muscle weakness was similar in the proximal and distal muscles. Grasping pain in the upper and lower limbs was also present. Neck flexor/extensor muscles were well preserved, and the patient could easily lift his neck. Dysphagia was not observed.

The patient’s level of consciousness was clear. No paralytic or sensory disorder was observed. In addition, cranial nerve impairment and dysarthria were not detected. Stocking and glove distribution of sensory loss were also not observed. However, the patient complained of limb pain but did not complain of numbness, a burning sensation, or pain in his hands and feet. We could not identify swelling of his joints, muscles, or superficial lymph node. Swelling of his left knee was not obvious at admission.

No eruption or erythema were observed, nor was Gottron’s sign detected. The results from the complete blood count, biochemical, coagulation, urinalysis, cerebrospinal fluid (CSF), and endocrinological tests are shown in Table 1. The white blood cell (WBC) count and C-reactive protein (CRP) levels were elevated. A slight abnormality in the liver function test was also found. The creatinine kinase (CK) level was normal at admission, and no electrolyte disorder was identified. Urinary testing did not suggest the presence of glomerulonephritis. A cerebrospinal fluid examination was also normal. In addition, the thyroid function and adrenal gland function were within normal ranges (Table 1); however, chest X-ray showed a mild emphysematous change. Consistent with this, computed tomography (CT) showed emphysematous changes and a solitary hepatic cyst. No interstitial pneumonia was detected. Electrocardiogram (ECG) testing showed normal sinus rhythm. Cardiac ultrasound showed good wall motion without vegetation or pericardial effusion. The patient was admitted for a further examination to focus on inflammation and the cause of his

Table 1. Laboratory Data at Admission.

| WBC 20,600 /μL | TP 6.3 g/dL | IgG 862 mg/dL | Color clear |
|----------------|------------|---------------|-------------|
| Neu 90.5 %     | Alb 2.9 g/dL| IgA 350 mg/dL | Specific Gravity 1.005 |
| Lym 4.5 %      | T-bil 0.8 mg/dL | IgM 36 mg/dL | Glu 67 mg/dL |
| Mono 3.5 %     | AST 50 U/L | CH50 81.2 CH50/mL | Protein 17 mg/dL |
| Eos 1.0 %      | ALT 55 U/L | C3 183 mg/dL | LDH <1 /μL |
| RBC 474 ×10⁶/μL | LDH 151 U/L | C4 58 mg/dL | LDI 14 IU/L |
| Hb 14.4 g/dL   | γGTP 119 U/L | Vitamin B12 >1,500 pg/mL | CK 24 IU/L |
| Ht 44.2 %      | T-chol 166 mg/dL | Vitamin B2 123.2 ng/mL | <Endocrional Data> |
| MCV 93.1 fl    | TG 157 mg/dL | Vitamin B1 107 ng/mL | ACTH 5.9 pg/mL |
| MCH 30.3 pg    | BUN 24.3 mg/dL | Folate 4.3 mg/mL | Cortisol 32.4 μg/dL |
| MCHC 32.6 %    | Cre 0.88 mg/dL | <Urinalysis> TSH 0.763 μIU/mL |
| Plt 58.8 ×10⁹/μL | Na 130 mEq/L | Specific Gravity 1.017 | fT3 1.14 ng/mL |
| ESR 1h 63 mm   | K 5.3 mEq/L | pH 5.5 | fT4 1.45 ng/dL |
| 2h 72 mm       | Cl 94 mEq/L | UP +/- | |
| <Coagulation>  | Ca 8.7 mg/dL | Glu | |
| PT-INR 1.25    | Glu 111 mg/dL | Nitrate | |
| PT-INR 43.7 sec | Glu 111 mg/dL | Nitrate | |
| Fibrinogen 929 mg/dL | HbA1c 6.0 % | <Urine Sedimentation> CRP 30.5 mg/dL uRBC 5-10 /HPF |
| Ferritin 816 ng/mL | uWBC 1-4 /HPF |
| Aldolase 6.6 U/L | | |

WBC: white blood cell count, RBC: red blood cell count, Hb: hemoglobin, Ht: hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, Pt: platelet, ESR: erythrocyte sedimentation ratio, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, T-Bil: total bilirubin, D-Bil: direct bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, γ-GTP: γ-glutamyl transpeptidase, T-Chol: total cholesterol, TG: triglyceride, BUN: blood urea nitrogen, Cr: creatinine, UA: uric acid, CK: creatine kinase, Glu: glucose, CRP: C-reactive protein, Ig: immunoglobulin, UP: proteinuria, uOB: urine occult blood, ACTH: adrenocorticotropic hormone, TSH: thyroid-stimulating hormone, fT3: free triiodothyronine, fT4: free thyroxine

The patient’s height was 163 cm, and he weighed 61.9 kg. Involuntary weight loss was not reported. His blood pressure was 162/102 mmHg, heart rate was a regular 109 beats per minute, and body temperature was 37.5 °C. He reported not feeling cold. His respiratory rate was 16 breaths per minute. SpO₂ was 97% in room air. A physical examination showed no remarkable findings expect for muscle weakness and tenderness. Manual muscle testing (MMT) was 4/5 for both his upper and lower limbs. The detailed MMT results were as follows: MMT (R/L) trapezius 4/4, deltoid 4/4, biceps 4/4, triceps 4/4, brachioradialis 4/4, iliopsoas 4/4, quadriceps 4/4, hamstrings 4/4, anterior tibialis 4/4, and gastrocnemius 4/4. The extent of muscle weakness was similar in the proximal and distal muscles. Grasping pain in the upper and lower limbs was also present. Neck flexor/extensor muscles were well preserved, and the patient could easily lift his neck. Dysphagia was not observed.

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Table 2. Laboratory Data of Infectious Disease Tests and Autoimmune Antibodies.

| Infectious Disease Test | Autoimmune Antibody |
|-------------------------|----------------------|
| PRP                     | ANA                  |
| TPHA                    | ds-DNA IgG           |
| HBsAg                   | Anti-RNP Ab          |
| HCV                     | Anti-SS-A-Ab         |
| ATLs                    | Anti-SS-B-Ab         |
| HIV                     | Anti-Jo-1-Ab         |
| Blood Culture           | Anti-CCP-Ab          |
| CSF Culture             | Anti-Centromere-Ab   |
| Urine Culture           | PR3-ANCA             |
| β-D-glucan              | MPO-ANCA             |
| QTF                     | Anti-GBM-Ab          |
| PCT                     | Anti-AchR-Ab         |
| Clq                     | MMP-3                |
| Cryoglobulin             | 213 ng/mL            |
| Anti-CLβ2GPI-Ab         | Clq                  |
| Anti-Cardiolipin-Ab     | <0.2 U/mL            |
|                        | <1.5 µg/mL           |
|                        | negative             |
|                        | 1.2 U/mL             |
|                        | 8.0 U/mL             |

ANA: anti-nuclear antibodies; Ab: antibody; ds-DNA: double-stranded DNA; RNP: ribonucleoprotein; SS: Sjogren syndrome; CCP: cyclic citrullinated peptide; PR3: proteinase-3; ANCA: anti-neutrophil cytoplasmic antibody; MPO: myeloperoxidase; GBM: glomerular basement membrane; AchR: acetylcholine receptor; MMP: matrix metalloproteinase; CLβ2GPI: cardiolipin antibody/β2-glycoprotein-1

Figure 1. MRI of the lower limb. Diffuse edematous changes were identified on the bilateral leg. An increased T2 signal in the subcutaneous and deep fascia was not noticeable.

muscle weakness and tenderness.

We initially suspected infection (including rickettsia) or alcoholic myopathy and initiated administration of ampicillin/sulbactam and minocycline. Two days after admission, the blood culture and cerebrospinal fluid (CSF) culture results were shown to be negative. Other cultures also failed to show bacterial growth. However, the patient’s symptom did not change (Table 2). On day 5, the CK levels increased to 713 U/mL. Magnetic resonance imaging (MRI) of the lower limb showed diffuse high intensity on T2-weighted imaging (Fig. 1). On the 6th day after admission, his muscle weakness progressed, and the pain levels increased. On the 8th day, the patient’s symptom continued to worsen. The serum CK levels increased to 19,430 U/mL, and MMT of the limbs decreased to 2/2. The MMT result details are as follows: MMT (R/L) trapezius 2/2, deltoid 2/2, biceps 4/4, triceps 2/2, brachioradialis 2/2, ilopsoas 2/2, quadriceps 2/2, hamstrings 2/2, anterior tibialis 2/2, and gastrocnemius 2/2. The degree of muscle weakness was similar in the proximal and distal muscles. The patient reported pain in the extremities as intense; however, no sensory disorders were detected. The consciousness level was clear. The neck flexor/extensor muscles were not affected, and dysarthria and dysphagia were not obvious. Cranial nerve disorder was also not apparent. The patient could describe his symptoms by himself. Dark urine was observed on day 8. Serum CK levels increased to 29,998 IU/mL, and serum creatinine levels increased to 1.34 mg/dL. We performed a muscle biopsy of
the left gastrocnemius on day 8. On the same day, the prote- 
inase 3 (PR3)-ANCA titer was found to be 65.8 U/mL. In 
contrast, the results for other auto-antibodies, including 
myeloperoxidase (MPO-ANCA), were negative (Table 2). 
We hypothesized that the cause of muscle weakness and 
pain was related to vasculitis, so methylprednisolone 
(mPSL) pulse therapy was started.

The patient’s symptoms improved after treatment, and CK 
levels gradually decreased (Fig. 2). MMT recovered to 4/4. 
The detailed MMT results are as follows: MMT (R/L) trape- 
ziius 4/4, deltoid 4/4, biceps 4/4, triceps 4/4, brachioradialis 
4/4, iliopsoas 4/4, quadriceps 4/4, hamstrings 4/4, anterior 
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weakness was similar in both the proximal and distal mus- 
cles.

The muscle specimen showed severely degenerated mus- 
cle fiber surrounded by infiltrated neutrophils; few CD8- 
positive cells were detected (Fig. 3). Arterioles were nar- 
rowed due to intimal proliferation, and fibrinoid necrosis 
was identified (Fig. 4). Breakdown of the elastic lamina of 
the arteries was also observed (Fig. 5).

We concluded that these findings were compatible with 
vasculitis. We gradually reduced the dose of oral predniso-
lone. To control vasculitis, cyclophosphamide pulse (10 mg/ 
kg) therapy was administered on days 40 and 72. The pa-
tient was transferred to another hospital to continue rehabili-
tation on day 92. The patient underwent monthly intrave-
nous cyclophosphamide (IVCY) 10 times and had an un-
eventful course without any complications.

Figure 2. Clinical course. The y-axis on the left side shows the PR3-ANCA titer. The y-axis on the 
right side indicates the level of serum CK. CK was elevated on day 5 and peaked on day 11. The pro-
gression of muscle weakness and CK increase were highly correlated. The PR3-ANCA titer also 
decreased after treatment. After mPSL pulse therapy, CK gradually decreased to normal, and the mus-
cle strength returned.

Discussion

We report a case with an unusual presentation of vasculi-
tis that affected all limbs. Immunosuppressive therapy was 
successful in controlling the disease.

We first thought that this patient was affected by alcoholic 
myopathy, infectious myopathy, or polymyositis/dermatomyo-
sitis (PM/DM). The patient had a history of substantial 
alcohol consumption, which was discontinued after hospi-
talization. Alcohol withdrawal symptoms were not observed. 
Previous reports suggest that the discontinuation of alcohol 
consumption improves symptoms (13-15). However, our 
case did not reveal any improvement after the cessation of 
alcohol intake. As such, the possibility of alcoholic myopa-
thy was considered to be low.

We also considered infection-related myopathy. Many vi-
rnal infections are known to cause myositis with rhabdomy-
olysis, such as influenza A, B, and H1N1 (subtype of influ-
enza A virus) (16, 17); coxsackievirus (18); Epstein-Barr vi-
rus (19); herpes simplex virus (20); parainfluenza (21); ade-
novirus (22, 23); echovirus (24); cytomegalovirus (25); mea-
sles (26); varicella-zoster (27); human immunodeficiency vi-
rus (28, 29); and dengue (30). We could not assess the pres-
ence of antibodies against all of these diseases; however, 
HIV infection was indicated to be negative by serology. For 
viral infection, specific therapies seldom exist.

As an alternative diagnosis, we also considered scrub ty-
phus (a mite-borne infectious disease caused by Orientia 
tsutsugamushi). Although the patient did not show signs of a
Figure 3.  
A: Hematoxylin and Eosin (H&E) staining section of gastrocnemius revealed severely degenerated muscle fiber surrounded by infiltrated inflammatory cells, mainly neutrophils. (low-power field).  
B: H&E staining section of gastrocnemius. (high-power field). Degenerated muscle fiber (arrow) surrounded by infiltrated inflammatory cells (arrowhead).  
C: Myeloperoxidase (MPO) staining; MPO-positive cells (neutrophils) had infiltrated.  
D: CD8 staining. Few CD8-positive cells (lymphocyte) were observed.

Figure 4.  
A: Elastica-Masson (EM) staining. Fibrinoid necrosis was found in the arteriole wall (arrow).  
B: An EM-stained section revealed small-artery stenosis by intimal proliferation (arrow).

rash or lymphadenopathy, he did have a fever and mild liver function abnormalities. We performed a thorough examination to find any evidence of bites, but none could be identified. We started minocycline empirically, but the patient’s symptoms did not improve.  

Tsutugamushi IgM and IgG were not elevated. Although the patient did not show typical symptoms of pneumonia or acute pyelonephritis, we could not exclude the possibility of bacterial infection. After performing blood cultures and the QuantiFERON-3 G test, we empirically started ampicillin/sulbactam, but the patient’s symptoms did not improve.

We also assessed the possibility of drug-induced vasculitis/rhabdomyolysis. Allopurinol was discontinued before admission, and we believe it was involved to a slight extent. Ampicillin/sulbactam and minocycline were started on the day of admission. These drugs may have caused rhabdomy-
We therefore started the patient on immunosuppressant therapy, which proved highly effective. We concluded that the muscle was the main cause of the weakness.

Several studies have reported vasculitis limited to the limbs. Miyashita et al. reported 7 cases of lower limb-restricted vasculitis (10), and Khellaf et al. reported 11 cases of lower limb-restricted vasculitis (11). In these reports, the upper limbs were not involved. Nadja et al. also reported three cases of muscle-limited vasculitis (12). These studies support our diagnosis of limb-limited vasculitis. Previous reports were unable to distinguish PN from AAV. We next considered the type of vasculitis in our case. According to the Watts criteria for the classification of vasculitis, our case was classified as microscopic polyangiitis (MPA) (41). Our case was not accompanied by eosinophilia or granuloma in the biopsy specimens. A muscle biopsy showed inflammation of both the arterioles and medium-sized arteries and was positive for PR3-ANCA. These data are more closely compatible with MPA than PN.

Alternatively, this may be a case of polymyositis (PM). As mentioned above, the clinical presentation mostly satisfied the diagnostic criteria of PM. However, some characteristics were different from those of PM. PM is thought to primarily cause muscle weakness in the proximal muscles. Instead, our case showed similar muscle weakness in both the proximal and distal muscles. Thus, on this clinical point, this case differed from that expected of PM. Furthermore, regarding the pathology of our case, several results differed from those expected if the patient had PM. For example, PM muscle pathology is characterized by cellular infiltrate (predominantly macrophage and lymphocyte) in the muscle fiber and no signs of vasculopathy (41, 42). In contrast, as shown in Fig. 3, we found that inflammatory cell infiltration was localized around the muscle fiber, and minimal cell infiltration was observed in the muscle fiber. Neutrophils were the predominant cell type present in the specimens (Fig. 3), and arteriole occlusion was observed (Fig. 4, 5). These findings support the diagnosis of vasculitis and the involvement of arterioles.

In contrast, PN usually affects medium-sized vessels (di-

ology in this patient. Indeed, all drugs have the potential to cause rhabdomyolysis. We therefore cannot absolutely rule out the possibility of antibiotic-related rhabdomyolysis. However, the patient’s symptoms gradually progressed before admission, and the patient was already affected by vasculitis upon admission. As one hypothesis, antibiotics might have exacerbated vasculitis in this case. In particular, minocycline can sometimes cause vasculitis (31). It is therefore possible that antibiotics might have exacerbated the patient’s vasculitis.

Autoantibody titers did not show any increases, with the exception of PR3-ANCA. Increased ANCA titers are sometimes a false-positive result, especially if several organs are involved (32). For example, inflammatory bowel disease, infection, and malignancy occasionally result in an elevated ANCA titer (32). In Japan, AAV primarily targets the kidneys, lungs, and nervous system (33). There was a lack of convincing evidence that the patient’s muscle pain and weakness were due to autoimmune disease. The patient’s clinical symptoms satisfied some of the criteria for polymyositis, such as muscle weakness and pain, elevated serum CK levels, absence of arthritis, presence of systemic inflammation, and muscle fiber degeneration, and inflammatory cell infiltration (34-36). In polymyositis, it is unusual for the Jo-1 antibody to be negative and PR3-ANCA levels to be elevated.

In the present case, muscle weakness progressed rapidly, and we were unable to wait until a perfect diagnosis could be made. We therefore started the patient on immunosuppressant therapy, which proved highly effective.

We examined the validity of our diagnosis of vasculitis. Systemic vasculitis sometimes involves peripheral neuropathy (37-39). Suppiah et al. reported that the incidence of vasculitis motor-involving neuropathy was between 7% of microscopic polyangiitis (MPA) and 7% of granulomatosis with polyangiitis (GPA). About 50%-75% of cases with polyarteritis nodosa (PN) involve the peripheral nervous system (38). These studies examined peripheral neuropathy as a systemic symptom (39). However, nephropathy was not accompanied by elevated CK levels. We were able to confirm muscular degeneration by MRI and a biopsy in this case.

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Figure 5. A: EM staining. Breakdown of the elastic lamina arteriole was detected (arrow). B: An EM-stained section revealed breakdown of the elastic lamina of a medium-sized artery (arrow).
ameter 100-150 μm), and this finding was also observed in our case. However, according to the Watts algorithm, MPA was classified before PN. Taking these findings together, we conclude that this patient was affected by MPA. However, the coexistence of MPA and PN cannot be ruled out.

Another differential diagnosis that needed to be excluded was neutrophilic myositis, which sometimes accompanies ulcerative colitis and celiac disease (43, 44). However, our case did not show colitis or other celiac disease, and the disease background differed from those in previous reports (43, 44). Previous reports of neutrophilic myositis did not show accompanying vasculitis. The question we addressed was where was the main location of inflammation in this case—the vessel or the muscle itself. We understand that it is impossible to perfectly classify the location of inflammation. Prayton reported that necrotizing myositis was mainly caused by vessels, whereas degenerate and/or regenerate muscle fibers were mainly caused by neurogenic disorders (45). One suggestive case report by Parent et al. described a case of eosinophilic granulomatosis with polyangiitis (EGPA) presenting as diffuse myositis. In that report, a muscle biopsy showed necrotizing vasculitis with true myositis (46), and the main location of inflammation was thought to be both the vessels that supply the muscles and the muscle itself. Our case shows that both perimysial and endomysial infiltration of neutrophils can accompany vasculitis (Fig. 3A, 3B). The progression of the disease was rapid (Fig. 2). Inflammation of the vessels gradually narrowed the arteries, which became occluded. This interpretation seems to match the pathological mechanism identified in our case. Perimysial and endomysial infiltration of neutrophils may be a result of infarction or the spread of vasculitis. Taking these findings together, multiple small infarctions of the artery supplying skeletal muscles were the main cause in our case. The further examination of similar diseases is necessary to elucidate the pathological mechanism involved.

Previous reports have shown that immunosuppressive treatment (steroid and/or cyclophosphamide) was successful in controlling the disease (10-12). Since vasculitis limited to the muscle is extremely rare, we were unable to anticipate the prognosis of this case. Careful observation for relapse of the disease is needed.

In conclusion, we herein reported a case of MPA limited to muscle symptoms (pain and weakness). Our patient responded well to steroid and cyclophosphamide therapy. In the Ishinomaki region, the incidence of MPA increased after the Great East Japan earthquake (47). As the incidence of MPA increases, the number of cases with variable MPA phenotypes will also increase. This unusual case may help minimize the possibility of a missed diagnosis of AAV.

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

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Ethics Committee Approval: Informed consent was obtained from the patient. All procedures were carried out in accordance with the Declaration of Helsinki.

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