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Atypical Hemolytic Uremic Syndrome With the p.Ile1157Thr C3 Mutation Successfully Treated With Plasma Exchange and Eculizumab: A Case Report

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Objectives: To describe a case of atypical hemolytic uremic syndrome induced by influenza A infection with the p.Ile1157Thr C3 mutation.

Data Sources: Clinical observations of a patient.

Study Selection: Case reports.

Data Extraction: Data extracted from medical records, after patient's consent.

Data Synthesis: Four days prior to presentation to our hospital, a 16-year-old adolescent had a fever and arthralgia with hematuria. He was found to be positive for type A influenza and prescribed oseltamivir and acetaminophen by a primary-care physician. A bleeding tendency and purpura in the extremities and on the trunk developed; therefore, he was transferred to Chiba University Hospital. Hematology revealed severe thrombocytopenia, hyperbilirubinemia, and acute kidney injury. Aspartate aminotransferase, lactate dehydrogenase, and potassium could not be determined because of severe hemolysis. Highly elevated blood urea nitrogen and creatinine levels indicated acute kidney injury. A platelet count of 24,000/μL indicated thrombocytopenia, with low hemoglobin level. Peripheral blood profiling identified schistocytes. Continuous hemodiafiltration and plasma infusion were initiated immediately; however, he became oliguric. Plasma exchange was initiated on ICU day 3, but decreased urine output, hemolysis, and thrombocytopenia persisted. IV eculizumab therapy was initiated on day 7 and resulted in recovery of these symptoms and also successful discontinuation of renal support. The patient showed a stable condition without recurrence of hemolytic findings and acute kidney injury and is currently on maintenance therapy of eculizumab (1,200 mg, every other week) without any relapse of atypical hemolytic uremic syndrome symptoms. A plasma sample collected prior to initiation of plasma exchange showed an disintegrin-like and metalloprotease with thrombospondin type 1 motifs 13 activity level of 104.9 %. The absence of both Shiga toxin-producing *Escherichia coli* in feces led to suspicion of atypical hemolytic uremic syndrome. Subsequent genetic analysis identified a mutation in *C3* (p.Ile1157Thr), confirming the diagnosis of atypical hemolytic uremic syndrome.

Conclusions: Although managing thrombocytopenia secondary to infection, inclusion of atypical hemolytic uremic syndrome in the differential diagnosis at an early stage is important in clinical practice.

Key Words: acute kidney injury; atypical hemolytic uremic syndrome; complement; genetics; plasma exchange

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Atypical hemolytic uremic syndrome (aHUS) is a thrombotic microangiopathy (TMA) characterized by three major signs: microangiopathic hemolytic anemia, consumptive thrombocytopenia, and organ dysfunction caused by microvascular platelet thrombi. The typical variants of TMA are hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). The development of HUS is mainly induced by Shiga toxin-producing *Escherichia coli* (STEC) strains, while the main etiology of TTP is reduced activity of a disintegrin-like and metalloprotease with thrombospondin type 1 motifs 13 (ADAMTS13). Additionally, non-diarrheal HUS and a familial form of HUS have also been known and are categorized as aHUS. Studies of the pathophysiology of aHUS involving genetic analysis and other methods revealed that the etiology of aHUS (in a narrow sense) involves congenital or acquired abnormalities in complement pathway activation (1).

aHUS is associated with the failure of various organs, particularly renal dysfunction, which occurs at high frequencies. Because delayed treatment of aHUS may lead to renal death and therefore can be fatal, early diagnosis and treatment are essential.

Here, we report a case of aHUS triggered by type A influenza infection in which remission was achieved by plasma exchange and eculizumab administration.

CASE PRESENTATION

The patient was a 16-year-old adolescent weighing 63.5 kg. The patient had a history of bronchial asthma and a history of measles and febrile seizure (without recurrence) in childhood. The patient's younger sister had a history of hematuria of unknown etiology.

Four days prior to presentation to our hospital, the patient had a fever and arthralgia with hematuria. Three days prior, he consulted a primary-care physician. He was found to be positive for type A influenza by influenza antigen testing and prescribed oseltamivir and acetaminophen. Two days prior, symptoms suggesting a bleeding tendency (such as bloody sputum and epistaxis) developed. One day prior to presentation to our hospital, purpura developed in the upper and lower extremities and on the trunk. No gastrointestinal symptoms such as diarrhea were observed during the clinical course until this time point. On the day of presentation to Chiba University Hospital, he consulted the primary-care physician again. Physical examination revealed jaundice and oral hemorrhage. Hematology revealed advanced thrombocytopenia, hyperbilirubinemia, and acute kidney injury.

Clinical Course

Upon presentation to Chiba University Hospital, the patient was fully conscious with no abnormal vital signs (body temperature, 36.9°C; heart rate, 54/min; blood pressure 149/56 mm Hg; oxygen saturation, 98% on room air; respiratory rate, 19/min). In hematologic examination, aspartate aminotransferase, lactate dehydrogenase, and potassium could not be determined because of hemolysis. Blood urea nitrogen (BUN) (107 mg/dL) and creatinine (8.03 mg/dL) levels indicated severe acute kidney injury. A platelet count of 24,000/μL indicated thrombocytopenia, with hemoglobin and hematocrit levels of 11.0 g/dL and 31%, respectively. Peripheral blood profiling identified red cell fragmentation (2.3%). Blood coagulation tests showed no apparent abnormalities (international normalized ratio of prothrombin time, 1.0; activated partial thromboplastin time, 27.0 s [reference range, 25.1–40.7 s]; fibrinogen, 222 mg/dL), therefore disseminated intravascular coagulation was ruled out (2). Complement assay (complement component 3 [C3] level, 74 mg/dL; complement component 4 level, 18 mg/dL) showed a slight reduction in C3 (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCX/A8; **legend**, Supplemental Digital Content 2, http://links.lww.com/CCX/A9). Rapid testing for influenza virus using a specimen obtained from the nasal mucosa showed positive results for type A virus.

To treat his acute kidney injury, renal replacement therapy with continuous hemodiafiltration was initiated. Because TTP could not initially be ruled out, fresh frozen plasma (6 U/d) as plasma infusion therapy was administered until assay results for ADAMTS13 activity were obtained. On day 2, further progression of anemia was observed (hemoglobin, 9.2 g/dL; hematocrit, 25.3%). Because hemolytic variables and acute kidney injury did not improve by day 3, plasma exchange therapy (total volume of plasma exchanged, 3,360 mL) was initiated and continued for three consecutive days until day 5. After plasma exchange therapy, lactate dehydrogenase decreased and hemolytic variables improved to some extent. Although the creatinine level was decreased to 3.18 mg/dL and weaning from continuous hemodiafiltration was successful, BUN and creatinine levels increased again and intermittent hemodialysis was required. On day 7, the ADAMTS13 assay results obtained using specimens submitted on day 3 confirmed negative results for the decrease in ADAMTS13 activity (ADAMTS13 activity, 104.9% [reference range, 70–120%]; ADAMTS13 inhibitor, <0.5 Bethesda units/mL), ruling out TTP. Because no gastrointestinal symptoms (such as diarrhea and hematochezia) were observed during the clinical course and stool culture with a specimen collected on hospital admission detected no pathogenic *E. coli* strains or Shiga toxin, the possibility of HUS was not supported. Thus, the patient was tentatively diagnosed with aHUS. On the same day, administration of eculizumab (900 mg) was initiated. On day 10, hematology analysis revealed increased BUN and creatinine levels and a second hemodialysis was performed. On day 14, hematology showed improved BUN and creatinine levels and the patient was weaned from hemodialysis. On day 12, negativity for anti-complement factor H (CFH) antibody was confirmed using a specimen submitted at hospital admission (3). Administration of eculizumab (900 mg) was repeated on days 14 and 21 (**Fig. 1**). The patient showed a stable condition without recurrence of hemolytic findings and acute kidney injury and was transferred to another medical institution near his home on day 25. He is currently being administered eculizumab therapy (1,200 mg, every other week) without any relapse of aHUS symptoms. Subsequent genetic analysis identified a mutation in *C3* (p.Ile1157Thr) (3, 4), confirming the diagnosis of aHUS although the patient was negative for anti-CFH.

DISCUSSION

In the present case, we indicated that the patient presented with TMA symptoms and was finally diagnosed with aHUS through genetic testing. Although STEC-HUS cases are associated with

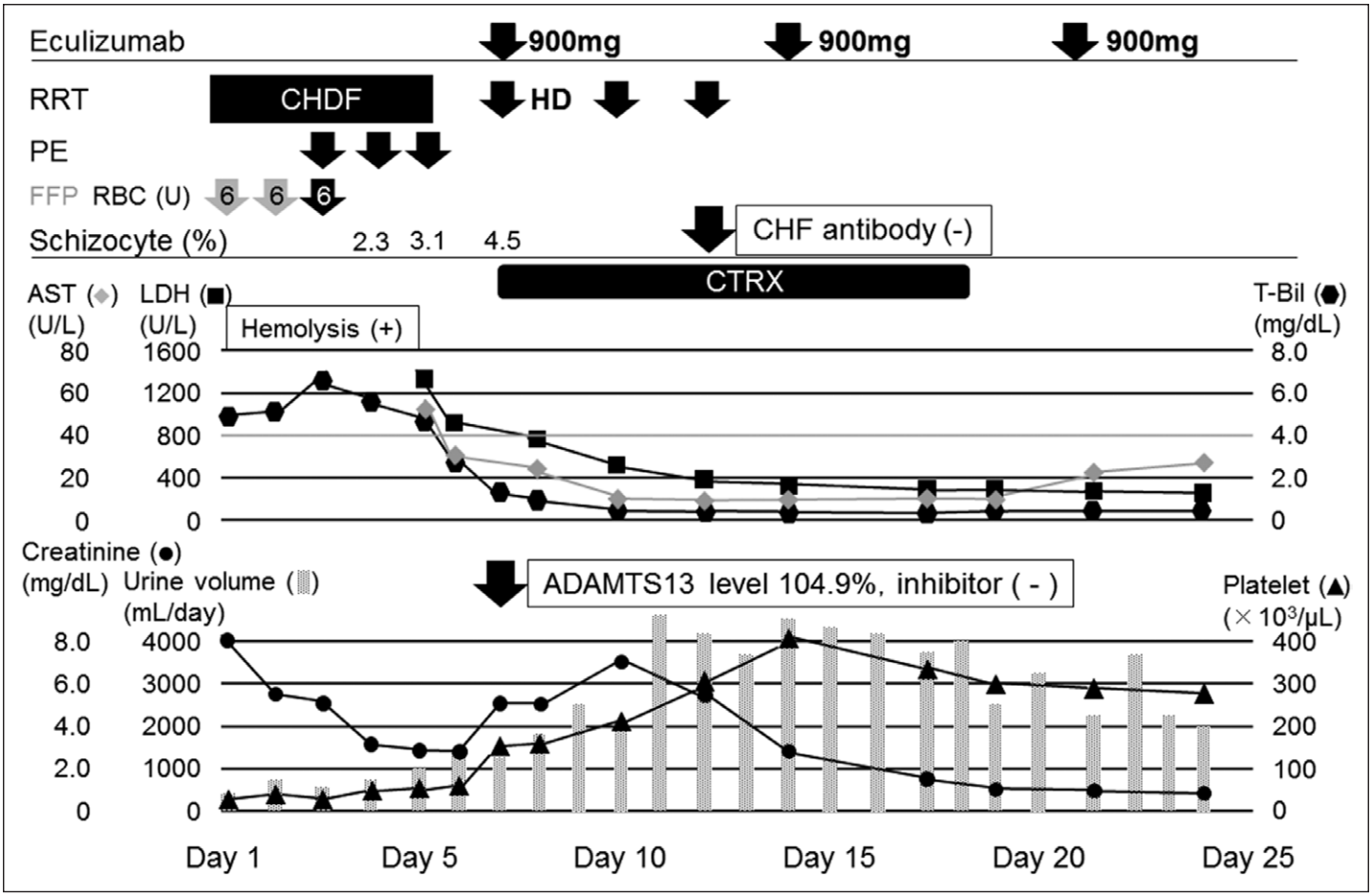

Figure 1. Clinical course. Continuous hemodiafiltration (CHDF) was introduced on ICU day 1. The patient remained thrombocytopenia and schistocytosis after 3 sessions of plasma exchange (PE) therapy. Eculizumab was introduced to address a decrease in platelet counts and also increase in serum creatinine levels on ICU day 7 in suspicion of atypical hemolytic uremic syndrome, and a increase in platelet counts and normalization of the other variables of thrombotic microangiopathy was observed on the next few days. Renal support was successfully discontinued. ADAMTS13 = a disintegrin-like and metalloprotease with thrombospondin type 1 motifs 13, AST = aspartate aminotransferase, CHF = complement factor H, CTRX = ceftriaxone, FFP = fresh frozen plasma, HD = hemodialysis, LDH = lactate dehydrogenase, RBC = red blood cells, RRT = renal replacement therapy, T-Bil = total bilirubin.

bloody diarrhea caused by infection with hemolytic *E. coli*, some cases of HUS are not. STEC-HUS is sometimes referred to as (post-) diarrheal or D(+)HUS, while the latter type is referred to as non-diarrheal or D(–)HUS (5). In 1981, Thompson and Winterborn (6) reported autosomal recessive inheritance of a genetic defect causing D(–)HUS in a family study of a patient with D(–)HUS and found reduced CFH levels in this patient. In 1998, Warwicker et al (7) demonstrated an association between genetic abnormalities in CFH and aHUS. Subsequently, genetic defects in genes encoding complement factor B (8), complement factor I (9), membrane cofactor protein (MCP) (9), C3 (10), thrombomodulin (11), and diacylglycerol kinase ε (12) were reported as congenital defects in complement-related genes. Additionally, anti-CFH antibodies were reported to be related to acquired deficiency of complement factors (13). The occurrence rate of aHUS is reportedly 0.4–2 cases per million population per year (14, 15), indicating that this disease is rare.

In the present case, a genetic mutation in *C3*, p.Ile1157Thr was identified, and this mutation has been reported to be a gain-of-function mutation (16). Multiple *C3* mutations have been reported (1, 10, 17–19) and are detected in 5–10% and 31% of aHUS cases in Caucasian and Japanese populations, respectively (20). Matsumoto et al (4) showed that the mutation *C3* p.Ile1157Thr has a relatively high frequency in Japan. In an aHUS patient with this mutation treated with eculizumab, laboratory variables improved promptly after treatment initiation (4). In our patient, a market increase in urine output was observed on the fourth day after eculizumab initiation. This prompt improvement of renal function is consistent with a finding in the previous report (21). On the other hand, some of the aHUS patients improved to remission and normal renal function without eculizumab (16). However, a patient with aHUS associated with a heterozygous mutation in the *C3* p.Ile1157Thr who experienced numerous relapses without eculizumab treatment was also reported (22). There is no report which clearly determine the discontinuance criteria of eculizumab therapy at this time.

Our patient harbored a *C3* mutation but exhibited a minimal reduction in blood C3 levels (74 mg/dL) in hematology on presentation to Chiba University Hospital. Although decreased C3 levels were observed in patients with *C3* mutations in some previous studies (23, 24), Noris et al (10) reported that some patients with *C3* mutations did not show markedly decreased blood C3 levels.

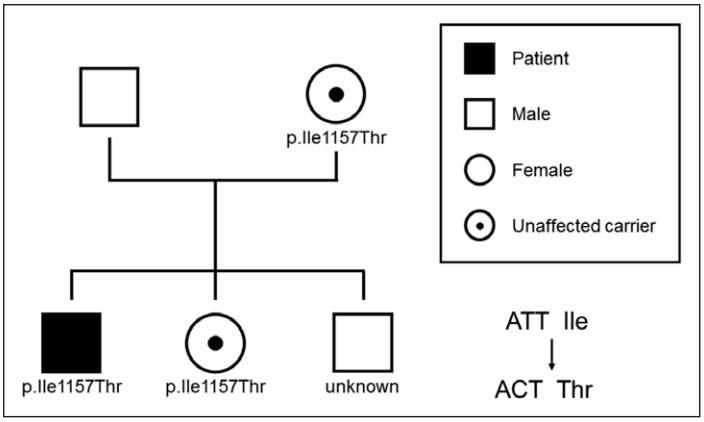

Figure 2. Family with a *C3*-p.Ile1157Thr mutation. A male patient developed atypical hemolytic uremic syndrome (aHUS) at the age of 16. His younger sister who also has a *C3*-p.Ile1157Thr mutation previously had a history of hematuria of unknown etiology. His mother with a *C3*-p.Ile1157Thr mutation has never had any symptoms suspected of aHUS. A = adenine, C = cytosine, Ile = isoleucine, T = thymine, Thr = threonine.

Thus, the blood levels of C3 do not always predict the *C3* mutation status (20).

C3 plays a central role in the complement system, which has classical, lectin, and alternate pathways. When individual pathways are activated, C3 is cleaved to generate C3b and C3a (an anaphylatoxin) (25). After a series of processing steps, C3a and C5a are formed, which have anaphylatoxin activities and cause inflammatory responses. C3b are inactivated by factors such as CFH and MCP. In aHUS patients with *C3* mutations, reduced binding activity or secretion of these proteins was observed (23). Additionally, reduced C3 activity was observed in aHUS associated with abnormalities in activation of the alternative pathway of the complement system. However, the frequency of reduced C3 activity varies depending on the *C3* mutation from 20% to 100% (4), while 20–30% of aHUS patients with *C3* mutations have normal C3 activity. Thus, the diagnostic value of C3 activity is low. In contrast, serum levels of C5b-9 are higher in aHUS than in TTP (26). An ex vivo study suggested that the degree of deposition of C5b-9 onto vascular endothelial cells is useful for evaluating complement activity and determining the therapeutic effect of eculizumab (27). The clinical usefulness of C5b-9 for diagnosing and treating aHUS requires further investigation.

Treatment for aHUS is generally initiated with plasma exchange therapy. In the present case, lack of improvement in renal function by plasma exchange and normal ADAMTS13 activity with negativity for ADAMTS13 inhibitor led to an early diagnosis of aHUS and immediate initiation of eculizumab administration. Based on this, an assay for ADAMTS13 activity should immediately be performed to ensure successful treatment of aHUS. This assay has been covered by the National Health Insurance in Japan since April 2018 and its utilization in clinical practice is encouraged. Eculizumab, a humanized monoclonal antibody against C5, inhibits the cleavage of C5 to C5a and C5b, thereby suppressing formation of the membrane attack complement complex. If plasma exchange performed for 3–5 consecutive days fails to stop progression of acute kidney injury, aHUS is strongly suggested (28, 29). We previously experienced a case of aHUS in which, after eight plasma exchange sessions failed to improve the patient's condition, eculizumab administration promptly improved renal function (30). Furthermore, Legendre et al (31) reported that initiation of eculizumab after progression to chronic renal injury failed to restore renal function, while earlier treatment successfully restored renal function. Thus, early diagnosis and treatment are important for managing aHUS.

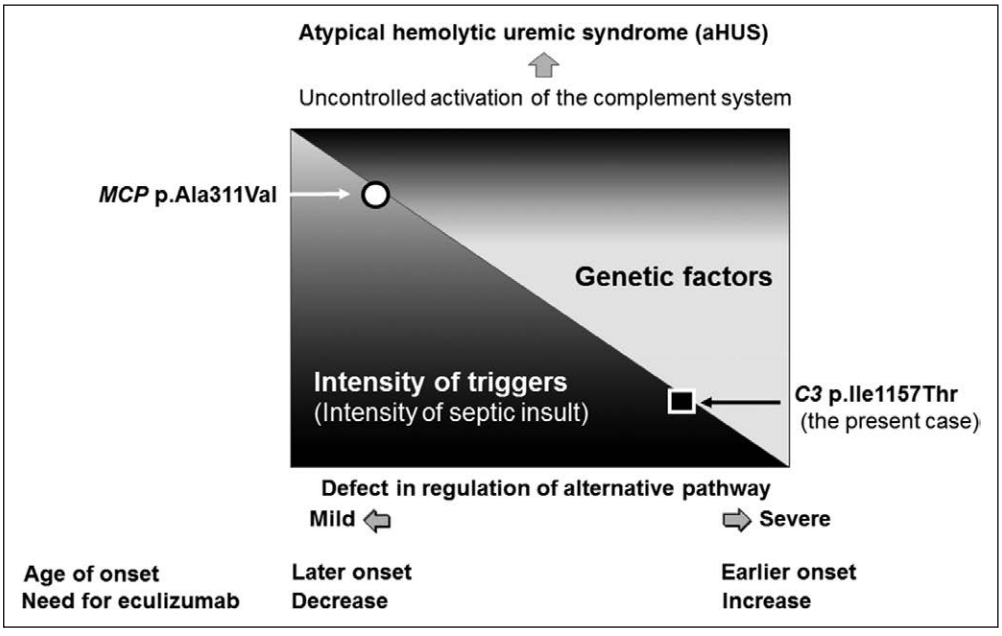

Figure 3. Position of the present case in the multiple hit hypothesis of atypical hemolytic uremic syndrome (aHUS) pathophysiology. Onset of aHUS is the consequence of the combination of genetic predisposition and trigger factors (35). The genetic predisposition can be mild or severe and *C3* p.Ile1157Thr is thought to be severe because onset of age is relatively younger (16). On the other hand, aHUS patients with a mutation of the gene of membrane cofactor protein (*MCP*) p.Ala311Val might be under the less genetic effect (30). It is thought to be proportionally necessary for more severe and/or younger patients to have eculizumab like the present case. *Black square*: 16-year-old male patient with *C3* p.Ile1157Thr; *white circle*: 62-year-old male patient with *MCP* p.Ala311Val (30). Ile = isoleucine, Thr = threonine.

In the field of emergency and critical care medicine, physicians encounter many conditions similar to aHUS, such as acute kidney injury caused by disseminated intravascular coagulation, indicating the importance of early diagnosis and treatment. Diagnostic criteria for aHUS are still under debate (2, 32).

In the present case, the patient's younger sister experienced hematuria of unknown etiology. Because familial cases of aHUS due to abnormal C3 with the p.Ile1157Thr mutation have been reported (15), we performed genetic screening of the patient's family members including his younger

sister with approval from the Institutional Review Board of Chiba University Hospital (Institutional Review Board Review Number 747(541)). A quantitative hemolytic assay using sheep RBCs (3) was negative for the patient and his younger sister, without excessive hemolysis (**Fig. 2**). This assay detects abnormalities in the alternative pathway of the complement system; particularly, individuals with abnormalities in the gene encoding Factor H and those positive for anti-Factor H antibodies show positive results (33). Genetic analysis identified the *C3* p.Ile1157Thr mutation (identical to the present case) in his mother and younger sister, but not in his father (Fig. 2). This genetic mutation was reported in multiple aHUS patients in Japan (most lived in Mie Prefecture, Kansai district) and its inheritance has been reported (20). Although the patient's mother and younger sister have not experienced aHUS yet, they show potential for developing aHUS triggered by infection, pregnancy, or immunization and should be closely monitored.

Because aHUS is an extremely rare disease with an annual prevalence as low as 3.3 per million in children younger than 18 years (34), continued accumulation of knowledge regarding patterns of disease onset and response to treatments under different genetic backgrounds will be essential for the development of future treatment strategies (**Fig. 3**). It is still controversial whether we need to infuse eculizumab to all the aHUS patients with the mutation *C3* p.Ile1157Thr (16). Prospective studies and meta-analyses stratified with each genotype are therefore warranted to confirm our findings and set guidelines for treatment, monitoring, and maintenance.

CONCLUSIONS

In the present case, TMA triggered by influenza infection was successfully treated by plasma exchange and eculizumab without sequelae, including renal dysfunction. Subsequent genetic investigation identified the *C3* p.Ile1157Thr mutation to establish a diagnosis of aHUS. Although managing thrombocytopenia secondary to infection, inclusion of aHUS in the differential diagnosis at an early stage is important in clinical practice.

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