Child Neurology: Pathologically Confirmed Thrombotic Microangiopathy Caused by Onasemnogene Abeparvovec Treatment for SMA

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Abstract

Onasemnogene abeparvovec is an adeno-associated virus vector-based gene therapy for spinal muscular atrophy (SMA). Although several cases of drug-induced thrombotic microangiopathy due to onasemnogene abeparvovec have been reported, none has been confirmed pathologically. Here, we present renal histopathologic findings of TMA due to onasemnogene abeparvovec. On day 5 after receiving onasemnogene abeparvovec, a 23-month-old girl with SMA type 1 developed thrombocytopenia, microangiopathic hemolytic anemia, liver dysfunction, acute kidney injury, and hypertension. She was diagnosed with TMA and received an increased dose of prednisolone, antihypertensives, diuretics, packed red blood cell and platelet transfusion, a single dose of eculizumab, 4 cycles of plasmapheresis, and intermittent and continuous hemodialysis. Her TMA resolved by day 30. On day 49, renal biopsy was performed. Light microscopy revealed proliferation of glomerular mesangial cells and matrix, with mesangiolysis, endothelial cell swelling, and partial double contours of the glomerular basement membrane. Electron microscopy showed endothelial injury, with edematous changes of the subendothelial spaces and neoformation of the basement membrane, without electron-dense depositions. These findings are compatible with the recovery phase of TMA. One year after drug administration, her motor function is improved. She can hold her posture against gravity and has neither dysphagia nor respiratory disturbance, but mild hypertension persists. Physicians should be vigilant regarding TMA as a severe side effect of onasemnogene abeparvovec treatment, especially when thrombocytopenia, hemolytic anemia, increased lactate dehydrogenase, or acute kidney injury is present.

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Teaching Points

- Physicians should be vigilant regarding TMA as a severe side effect of onasemnogene abeparvovec treatment.
- In cases of TMA after onasemnogene abeparvovec treatment, renal biopsy may help in estimating the long-term prognosis.

Case Presentation

When she was 6 months old, our patient was referred to our department with the chief complaint of hypotonia. She was diagnosed with spinal muscular atrophy (SMA) type 1 (0 copies of *SMN1* and 2 copies of *SMN2*) at age 7 months; no other preexisting condition was diagnosed. She received a total of 7 intrathecal doses of nusinersen, with doses at 7, 8 (twice), 9, 13, 17, and 21 months of age. At age 23 months, she was hospitalized to receive onasemnogene abeparvovec. At this time, because of nusinersen therapy, her CHOP-INTEND score[1] and HINE-2 score[2] had increased from 21 to 46 and from 9 to 19, respectively (Figure 1A). She was clinically stable, without any respiratory support. However, because of the invasiveness of intrathecal nusinersen dosage once every 4 months and because her parents felt that onasemnogene abeparvovec might be more effective than nusinersen,[3] we discontinued nusinersen in favor of onasemnogene abeparvovec. We followed the treatment guidelines for onasemnogene abeparvovec published by the manufacturer and the Japanese Society of Child Neurology. One week before onasemnogene abeparvovec administration, our patient developed an upper respiratory infection but recovered from those symptoms in a few days. The day before the administration, her blood pressure, urine tests, complete blood count, liver enzymes, kidney function, and troponin I concentration were within normal limits, and she began receiving prednisolone (1 mg/kg daily). The next day, our patient received onasemnogene abeparvovec IV at a dose of 1.1×10^{14} vector genomes per kilogram of body weight.

On day 5 after the administration, she vomited frequently. Hematology revealed thrombocytopenia, microangiopathic hemolytic anemia, liver dysfunction, and elevated lactate dehydrogenase (LDH; 2,183 U/L). Given these findings, we increased her prednisolone dose to 2 mg/kg daily. On day 6, she developed hypertension, subcutaneous bleeding, and prolonged bleeding after blood collection and was treated with antihypertensives, diuretics, and packed red blood cell and platelet transfusion. Beginning on day 8, she needed intermittent hemodialysis because of anuria, uremia, and hyperkalemia. No enterohemorrhagic *Escherichia coli* was detected from her stool culture. ADAMTS13 (a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13) activity was within normal limits. Her C4 and CH50 levels were slightly decreased, but C3 was normal. Given these findings, we suspected drug-induced thrombotic microangiopathy (DITMA). On day 9, our patient's LDH value peaked at 4895 U/L, and she received the first of 4 cycles of plasmapheresis. On day 13, we administered a single dose of eculizumab, which is effective for complement-mediated TMA.[4] On day 14, she was transferred to a pediatric intensive care unit to undergo continuous hemodialysis for 1 week because of congestive heart failure. Our patient continued to receive systemic management and supportive care, and by day 30, she was dialysis-free, and her TMA had resolved. Mild hypertension, proteinuria, and hematuria remained.

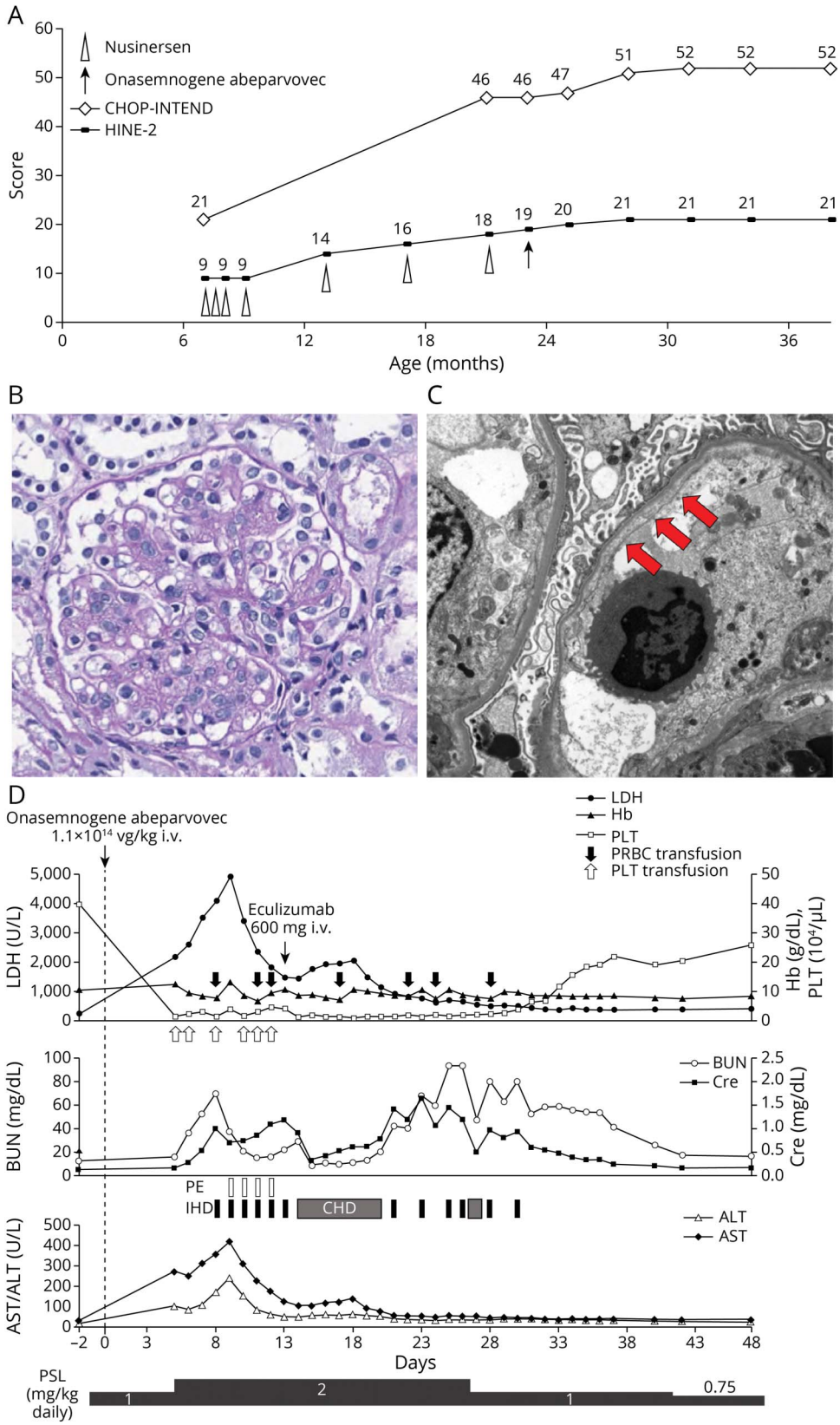
Our patient underwent renal biopsy on day 49. Light microscopy revealed proliferation of glomerular mesangial cells and matrix, with mesangiolysis, swelling of endothelial cells, and partial double contours of the glomerular basement membrane. Electron microscopy showed endothelial injury with edematous changes of the subendothelial spaces and neoformation of the basement membrane, without electron-dense depositions. Thus, her renal pathologic findings were compatible with the recovery phase of TMA[5] (Figure 1, B and C). She was discharged on day 51.

Figure 1D provides an overview of our patient's laboratory results and treatments. As her TMA and hepatic dysfunction decreased, we gradually decreased the prednisolone dose. Although liver enzyme concentrations increased transiently as the dosage decreased, prednisolone ultimately was discontinued after 4 months. Both hematuria and proteinuria had resolved by 5 months, but hypertension persisted 1 year later. We were concerned that the adverse reactions and their treatments might reduce the effectiveness of onasemnogene abeparvovec and that the prolonged hospitalization might lead to muscle weakness. However, at 1 year after administration, our patient's CHOP-INTEND and HINE-2 scores had risen to 52 and 21 points, respectively (Figure 1A).

Discussion

SMA is a neurodegenerative disease caused by homozygous loss of the survival motor neuron 1 (*SMN1*) gene. This gene encodes the survival motor neuron (SMN) protein, which is essential for the normal functioning and survival of motor neurons. SMA type 1 is a severe form of SMA, resulting in muscle weakness and severe wasting from early infancy and failure to achieve major motor milestones during development. The majority of SMA1-affected infants require feeding and ventilatory support by age 14 months and have a life expectancy of less than 2 years without intervention.[6] In 2016, the Food and Drug Administration (FDA) approved nusinersen, an antisense oligonucleotide.[7] In 2020, risdiplam, another small molecule, received FDA approval.[8] Onasemnogene abeparvovec, which was approved by the FDA in 2019, is an adeno-associated virus (AAV) vector-based gene therapy for SMA.[9] It delivers a fully functional copy of human *SMN1* via a self-complementary AAV9 vector. A 1-time IV administration of onasemnogene abeparvovec results in the production of the SMN protein in a child's motor neuron

Figure 1 Motor Function Scores, Renal Pathology Findings, and Clinical Course After Treatments



(A) Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) and Hammersmith Infant Neurological Exam Part 2 (HINE-2) scores. Arrowhead, administration of nusinersen; Arrow, administration of onasemnogene abeparvovec. (B) Light micrograph of renal biopsy tissue shows proliferation of mesangial cells and matrix with mesangiolysis. Periodic acid–Schiff stain; magnification 400×. (C) Electron micrograph of renal biopsy tissue shows edematous changes of the subendothelial spaces and neoformation of the basement membrane (red arrows), without electron-dense depositions. Magnification 12,000×. (D) Overview of laboratory results and treatments before discharge. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CHD, continuous hemodialysis; Cre, creatinine; Hb, hemoglobin; IHD, intermittent hemodialysis; LDH, lactate dehydrogenase; PE, plasmapheresis; PLT, platelets; PRBC, packed red blood cells; PSL, prednisolone; vg/kg, vector genomes per kilogram.

Table 1 Overview of Cases of TMA After the Administration of Onasemnogene Abeparvovec

Variable			This case	Case 1[12]	Case 2[12]	Case 3[12]
Country			Japan	United States	Australia	United States
Demographics			23 mo, female	5 mo, female	12 mo, female	14 mo, female
Patient weight at dosing			10.2 kg	6.5 kg	12.1 kg	8.7 kg
Time to onset and first symptom after onasemnogene abeparvovec			Day 5; vomiting	Day 7; hypertension, decreased urine output	Day 8; vomiting, reduced oral intake and urine output	Day 7; vomiting, dehydration
Nusinersen (most recent dose)			Yes (2 mo previously)	No	Yes (1 mo previously)	Yes (4 mo previously)
Concurrent infections			Upper respiratory infection 1 wk before dosing	Aspiration pneumonia 4 d before dosing	No	Urinary tract infection 3 d after presentation
Vaccines within 1 mo of onasemnogene abeparvovec			No	Yes (6 d after therapy)	Yes (10 d previously)	No
Laboratory evidence of TMA (baseline and after onasemnogene abeparvovec)	Hemoglobin (g/dL)	Baseline	10.6	10.3	11.4	12.5
		Nadir	5.7 (day 11)	7 (day 7)	9.6 (day 10)	6.1 (day 13)
	Platelet (K/μL)	Baseline	396	503	378	506
		Nadir	7	17	11	17
	Creatinine (mg/dL)	Baseline	0.1	0.1	0.28	0.1
		Peak	1.22	0.7	0.93	0.3
	LDH (U/L)	Peak	4,895	4,208	2,902	1,677
PT, PTT, and INR			Normal	Normal	Normal	Normal
Urinalysis			Protein, blood	Protein, blood	Protein, blood	Protein, blood
Investigations regarding acute complement pathway at presentation of TMA	C3		74.8 mg/dL (ref 65–135)	1.1 g/L (ref 0.9–1.8)	0.62 g/L (ref 0.72–1.64)	57.8 mg/dL (ref 90–180)
	C4		9.1 mg/dL (ref 13–35)	0.07 g/L (ref 0.15–0.57)	0.05 g/L (ref 0.14–0.42)	0.13 g/L (ref 0.15–0.57)
	CH50		30.7 mg/dL (ref 31.6–57.6)	160 U eq/mL (ref >70)	Not available	134 U eq/mL (ref >70)
Treatments	PRBC transfusion		Yes	Yes	No	Yes
	Platelet transfusion		Yes	Yes	No	No
	Increased dose of GC		Yes	Yes	Yes	Yes
	Plasmapheresis		Yes	Yes	No	No
	Dialysis		Yes	No	No	No
	Diuretic		Yes	Yes	Yes	Yes
	Antihypertensive		Yes	Yes	Yes	Yes
	Eculizumab		Single dose	No	No	Single dose
Other investigations	ADAMTS13		Normal	Normal	Normal	Normal
	Stool cultures		Negative	Negative	Negative	Negative
Outcome (time from diagnosis)			Recovered (4 wk) with persistent hypertension	Recovered (2 wk) with persistent hypertension	Recovered (4 wk)	Recovered (4 wk) with resolution of hypertension and nephrotic syndrome

ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; C, complement; GC,; INR, international normalized ratio; LDH, lactate dehydrogenase; mo, month; PRBC, packed red blood cell; PT, prothrombin time; PTT, partial thromboplastin time; ref, reference range.

cells.[10] Well-known side effects of the drug are fever, vomiting, acute liver injury, transient thrombocytopenia, and increased troponin I.[9]

TMA is characterized by its clinical presentation, which includes thrombocytopenia, microangiopathic hemolytic anemia, and organ damage including acute kidney injury. Primary acquired TMA syndromes include Shiga toxin–mediated TMA, ADAMTS13 deficiency–mediated TMA, complement-mediated TMA, and DITMA.[11] The current diagnosis criteria for TMA do not include renal biopsy. Although several cases of DITMA due to onasemnogene abeparvovec have been reported,[12] none provided pathologic confirmation or addressed the long-term prognosis. Because we needed to evaluate our patient's future treatment plan and prognosis in light of her renal pathology, we performed renal biopsy. The biopsy showed only a few sclerosing glomeruli, thus supporting the absence of diffuse global glomerulosclerosis and a relatively good prognosis without additional treatment.

We compare features of our current case of TMA caused by onasemnogene abeparvovec with 3 previously reported cases (Table 1).[12] None of the cases yielded enterohemorrhagic *Escherichia coli* from stool cultures. ADAMTS13 activity was normal in all 4 cases. Activation of the alternative complement pathway occurred in 2 of the 3 previous cases but not in our patient. Infection before or after administration of onasemnogene abeparvovec occurred in our patient and in 2 of the 3 previous cases. Immune responses to infection might have triggered the development of TMA.

Our patient received several doses of nusinersen before the administration of onasemnogene abeparvovec. We discontinued nusinersen after onasemnogene abeparvovec treatment in part because of limitations prescribed in the public health insurance of Japan. Two of the 3 previous cases were treated with nusinersen before onasemnogene abeparvovec.[12] Whether the preliminary administration of nusinersen in our patient led to a drug interaction with onasemnogene abeparvovec is unclear.

Treatment of DITMA consists of drug discontinuation and supportive care. As in our case, some patients have been treated with plasma exchange, anticomplementary therapy such as eculizumab, and immunosuppressive therapy such as increased glucocorticoid dosage. This combination therapy may be beneficial in cases of TMA due to onasemnogene abeparvovec, considering our patient's recovery from severe symptoms. DITMA has been classified into 2 categories: immune mediated and toxicity mediated.[13] The former leads rapidly to renal failure, whereas the latter has a course lasting over several weeks or months. Given the acute exacerbation of our patient's symptoms, we hypothesize that onasemnogene abeparvovec led to TMA via the immune-mediated mechanism. Among the 15 patients given AAV9 vector–based drugs in Duchenne Muscular Dystrophy clinical trials, 4 cases of TMA have been reported.[14] This finding suggests that ingredients common to both drugs may contribute to the induction of TMA. Likewise, hepatotoxicity, one of the major adverse events of onasemnogene abeparvovec, is thought to result from an immune response to AAV9 capsids.[15] However, considering the frequency, timing of onset, duration, and biodistribution of the drug,[4] the pathogenesis of drug-associated liver injury may be different from that of DITMA.

In the current case, TMA caused by onasemnogene abeparvovec was confirmed through pathology. We believe that the pathologic findings in this case report will help to elucidate the pathologic mechanism underlying DITMA due to onasemnogene abeparvovec. According to the manufacturer, as of July 2021, this drug has been administered in more than 1,400 cases of pediatric SMA, among which 9 cases of TMA have been documented.[14] TMA requires urgent treatment to avoid irreversible organ damage or death. Because it occurs in most patients after onasemnogene abeparvovec administration, thrombocytopenia alone is insufficient to prompt a suspicion of TMA. Particularly in children with previous nusinersen exposure, it is not uncommon for the platelet count to drop below 50,000/μL in the absence of TMA after onasemnogene abeparvovec administration.[3] Therefore, other potential signs of TMA should be monitored. Patients should be followed for signs of microangiopathic hemolytic anemia, such as anemia with crushed red blood cells, elevated LDH and indirect bilirubin, and signs of acute kidney injury, including hypertension, anuria, hematuria, elevated creatinine, and electrolyte abnormalities. Physicians should be vigilant regarding TMA as a possible severe side effect of onasemnogene abeparvovec treatment.

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Satoru Sakuma, MD, PhD	Department of Pediatrics, Osaka Metropolitan University Graduate School of Medicine	Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or intepretation of data; Other

Appendix *(continued)*

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