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A case of nonimmune hydrops fetalis that was successfully treated with ulinastatin

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Hydrops fetalis is usually resistant to treatment and is associated with a poor outcome. We report the successful treatment of nonimmune hydrops fetalis with ulinastatin, a urinary trypsin inhibitor. A male infant weighing 984 g was born at 31 weeks gestation by emergency caesarean section which had been performed because of fetal distress, oligohydramnios, and hydrops fetalis. Physical examination revealed generalised oedema and ascites. The cause of hydrops fetalis could not be identified. After initial stabilisation, hypoalbuminaemia and thrombocytopenia persisted despite repeated administration of 20% albumin and platelet concentrate, and were accompanied by disseminated intravenous coagulation (DIC). Upon administration of ulinastatin starting on day 7 of life, his serum albumin level and urine volume both increased, resulting in recovery from generalised body oedema. Ulinastatin also improved the DIC. This case suggests that ulinastatin exerts beneficial effects in patients with increased capillary permeability and reduced colloid osmotic pressure, with a resultant improvement of hydrops.

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Introduction

Nonimmune hydrops fetalis (NIHF) is a term that describes an oedematous fetus that does not have erythroblastosis fetalis from isoimmunisation. The cause of NIHF in 20-35% of cases can not be identified, and they are classified as "idiopathic"[1]. The mortality rate remains high because no specific management strategies have been established[2]. Ulinastatin (urinary trypsin inhibitor, ulinastatin) is an acid glycoprotein that is excreted in urine, and has a molecular weight of 67,000[3]. The specific activity of ulinastatin is 2,600 units/mg protein. One unit of ulinastatin inhibits 1 microg of trypsin. Ulinastatin has been reported to inhibit various enzymes and has been used clinically for the treatment of pancreatitis and circulatory shock[4,5]. It was recently used as an additional therapeutic approach to inhibit uterine contractions in order to prevent imminent premature delivery[6].

Case report

A 38 year old primigravida woman was admitted at 31 weeks and 5 days gestation for hydrops fetalis, intrauterine growth retardation, and oligohydramnios of unknown cause. Her pregnancy was uneventful up to the time of admission. Her laboratory evaluation was normal with a platelet count of 224,000/μl on the day of admission, and there was no evidence of rupture of membranes or viral infections. Maternal parvovirus B19 and cytomegalovirus infections were excluded based on the absence of specific immunoglobulin M in

the maternal serum. Fetal ultrasonographic evaluation on admission revealed ascites, generalised oedema, and cardiomegaly, although congenital heart defect and cardiomyopathy were excluded. In addition, M-mode fetal echocardiography was normal with no evidence of dysrhythmia as the cause of the generalised oedema.

An emergency cesarean section was performed at 31 weeks and 6 days gestation because of fetal distress. The male neonate was severely asphyxiated at birth. The Apgar scores at 1 and 5 minutes were 2 and 5, respectively. The birth weight was 984 g. Blood gas analysis revealed an umbilical cord pH of 7.18 and base excess of –9 mmol/l. The placenta was small (180 g weight) but had no gross abnormalities. The umbilical cord was short (21 cm length) but had no abnormal findings such as torsion or knot. After successful resuscitation including intubation and exogenous surfactant administration, he was placed on high-frequency oscillatory ventilation with 100% oxygen and inotropic support (dopamine and dobutamine each at an initial dose of 5 microg/kg/min) was started.

On physical examination, he had generalised oedema and abdominal distension with ascites, but had no anomalies. The chest X-ray showed cardiomegaly, but echocardiography did not reveal any cardiovascular abnormalities. The initial laboratory findings in the blood sample obtained at one hour after birth were as follows: white blood cell count, 4,600/µl; haemoglobin, 11.2 g/dl; haematocrit, 37.5%; platelets, 31,000/µl; plasma urea, 13.8 mg/dl; creatinine, 0.8 mg/dl; total protein, 3.2 g/dl; albumin, 2.1 g/dl; and C-reactive protein (CRP), <0.1 mg/dl. Karyotype analysis was normal.

After the initial management, his respiratory and circulatory conditions stabilised. However, hypoproteinaemia and hypoalbuminaemia persisted and his oedema progressively worsened. Repeated administration of 20% albumin on day 2 and days 5–8 did not increase the serum albumin level.

Thrombocytopenia also persisted, and his platelet count decreased to 16,000/µl on day 2. Transfusions of platelet concentrate were performed on days 3 (20 ml), 5 (15 ml), 6 (15 ml), 7 (30 ml), and 8 (15 ml). There was a small increase in the platelet count to 37,000/µl on day 4. Intravenous gammaglobulin (500 mg/day) was administered on days 3–5, but the platelet count did not significantly increase.

The creatinine level remained in the normal range over the first two weeks. On the 6th day of life, the diagnosis of disseminated intravascular coagulation (DIC) was confirmed, and replacement of fresh frozen plasma (10 ml/dose) and anti-coagulation therapy (1.3 mg/kg/h of nafamostat mesilate and 50 units/kg/day of antithrombin) were started. However, after receiving these therapies, his platelet count decreased.

Ulinastatin (15,000 units/kg/day) was administered from day 7 in an attempt to reduce capillary permeability and DIC. Ulinastatin was administered with informed consent from the parents because this drug was only licensed for acute circulatory insufficiency and pancreatitis in Japan. His urine volume significantly increased within one day of starting ulinastatin treatment and his serum albumin level and platelet count started to respond well to albumin replacement and platelet transfusion, respectively (Figures 1 and 2).

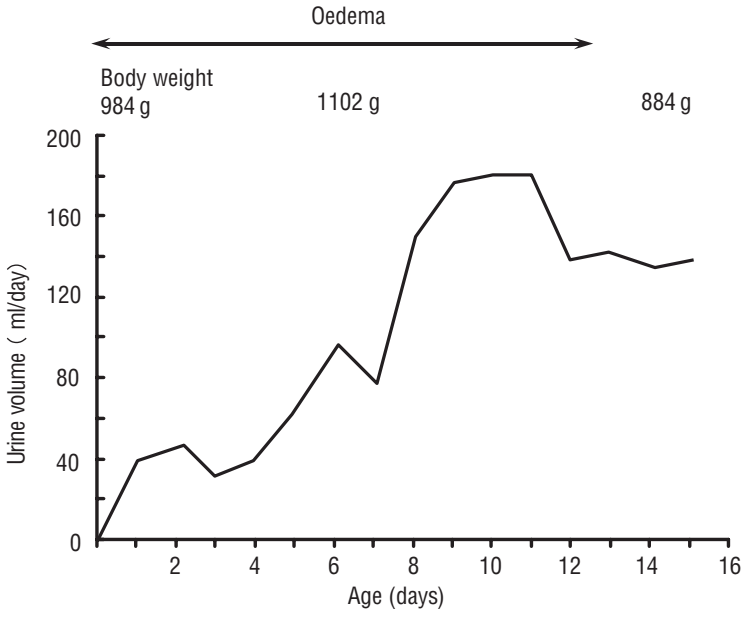

Figure 1 Clinical course of the patient depicting body weight and urine volume.

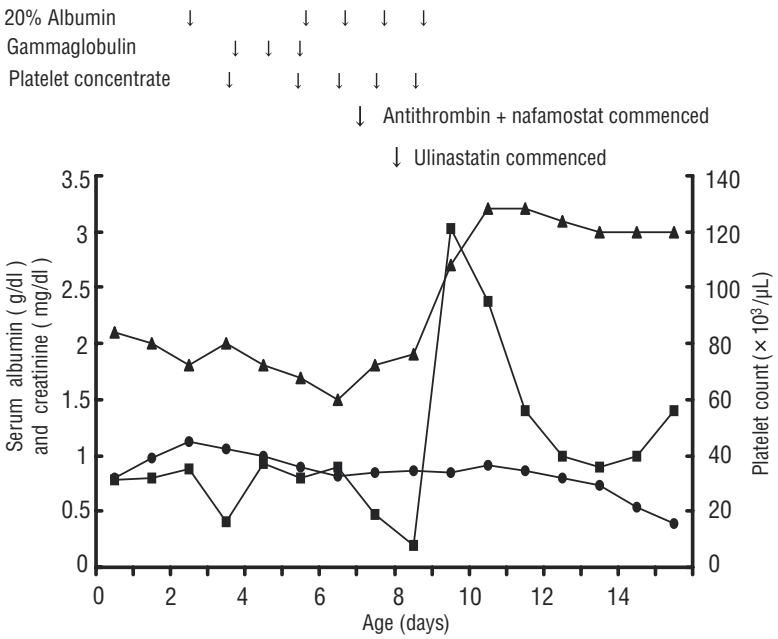

Figure 2 Changes in the platelet count (■), serum albumin(▲)and creatinine (●) in relation to therapy.

The serum total protein and albumin levels remained within the normal range after the second day of ulinastatin administration, and the generalised oedema resolved on day 12 of life. Ulinastatin administration was continued until day 20. The DIC also improved and platelet transfusions were discontinued on day 8. Thereafter, the patient had no major clinical problems and was discharged from the hospital at 101 days of age. The patient is currently 8 months old and growing well with no evidence of developmental delay.

Discussion

In newborns with NIHF, following initial stabilisation there are three main management problems. The first is inadequate ventilation due to persistent pulmonary hypertension (PPHN), which is usually present in infants with hydrops fetalis with pleural effusions. The second problem is generalised body oedema, which has been attributed to third spacing caused by a combination of low colloidal oncotic pressure and increased capillary permeability[7]. The third problem is DIC, which has been reported to occur in 50% of hydropic infants[8].

In our patient, the first problem was not serious because the patient did not have pleural effusions. Therefore, our therapeutic aims were to improve the increased capillary permeability and DIC, although we could not determine whether the DIC was due to asphyxia or hydrops. Exchange transfusion was considered as a treatment option, but it was not performed because it can lead to severe thrombocytopenia. Next, steroid administration was considered as a therapy that could probably improve the increased capillary permeability. However, we decided not to administer a steroid because of its tendency to cause infection, hypertension, hyperglycaemia, electrolyte imbalance, and gastrointestinal haemorrhage.

Then, we considered ulinastatin, which has a stabilising effect on the lysosomal membrane similar to steroids[4], and reduces capillary permeability, but has less side effects than steroids. It has been suggested that ulinastatin prevents DIC indirectly by inhibiting thromboplastin release[9]. There are no reports of ulinastatin administration for the treatment of NIHF, nor are there reports of steroid administration for NIHF. It was assumed that in the present patient, ulinastatin reduced capillary permeability, thereby increasing the blood pressure and heart rate as well as the intravascular volume. After ulinastatin administration was started, the serum albumin level tended to increase and albumin supplementation could be discontinued. Urine volume increased and the oedema gradually decreased. In addition, even though platelet transfusions were discontinued, the thrombocytopenia did not worsen and the DIC resolved.

In hydrops fetalis, tissue hypoxia due to fetal heart failure and circulatory insufficiency persisting from the fetal period leads to vascular endothelial cell injury, resulting in increased capillary permeability and DIC. Oxygen radicals produced by the hypoxic condition, macrophages, and the granulocyte elastase released from neutrophils that had been activated by cytokines, may promote the release of a chemical mediator that causes vascular

endothelial cell injury. Ulinastatin is an oxygen radical scavenger[10], and inhibits the synthesis of inflammatory cytokines[11], granulocyte elastase activity, and the activity of various proteases[12]. Ulinastatin may have protective effects against vascular endothelial cell injury.

The clinical course of the present patient improved after ulinastatin administration was started. However, there were no specific laboratory findings that demonstrated the effect of ulinastatin, and we did not determine the concentration of ulinastatin in either blood or urine. There is a possibility that other factors contributed to the recovery of the patient from hydrops fetalis, i.e. that the improvement was coincidental. It is suggested that ulinastatin not only improves circulatory insufficiency by reducing both capillary permeability and the plasma colloid osmotic pressure, but also contributes to the prevention of DIC in hydrops fetalis.

The general use of ulinastatin in children has not been established. Recently, particularly in Japan, ulinastatin has been used to treat Kawasaki disease. The efficacy of ulinastatin is dose-dependent, and it is now administered to patients with Kawasaki disease in Japan at a dose between 15,000 and 30,000 units/kg/day in which the dose for each patient is determined by trial and error[13]. Ulinastatin was recently administered to an infant at the age of 85 days, who had been born at 31 weeks gestation with a birth weight of 1,722 g and suffered from Kawasaki disease[14]. There are no reports of administration of ulinastatin to infants with hydrops fetalis or to extremely low birth weight infants. In the present case, we chose the dose of 15,000 units/kg/day, which had been determined based on the dosage for infants with Kawasaki disease.

Ulinastatin is thought to be a safe medicine for newborns and premature babies because there are few antigenic and toxic problems associated with its use and because the urine of fetuses and neonates contains a concentration of ulinastatin that is 100 times higher than that in the urine of adults[15]. Ulinastatin treatment may be an additional therapeutic approach to controlling NIHF, which has been resistant to pre- and postnatal treatments and is associated with a poor outcome. Controlled studies on ulinastatin in patients with NIHF are needed.

References

1 Bukowski R, Saade GR. Hydrops fetalis. Clin Perinatol 2000; 27: 1007-1031.
2 Wy CAW, Sajous CH, Loberiza F, Weiss MG. Outcome of infants with a diagnosis of hydrops fetalis in the 1990s. Am J Perinatol 1999; 16: 561-567.
3 Sumi H, Takada H, Takada A. Studies on human urinary trypsin inhibitor 1. Its modification on treatment of urine with acid. Thromb Res 1977; 11: 747-754.
4 Oda T, Miyawaki T, Sameshima T, Miyao J. Antishock effects of urinary trypsin inhibitor, MR-20 (in Japanese). Jpn J Anesthesiol 1984; 33: 137-142.
5 Shikimi T, Handa M. Inhibitory effect of human urinary trypsin inhibitor (ulinastatin) on lysosomal thiol proteinases. Japan J Pharmacol 1986; 42: 571-574.
6 Kanayama N, el Maradny E, Yamamoto N et al. Urinary trypsin inhibitor: a new drug to treat preterm labor: a comparative study with ritodrine. Eur J Obstet Gynecol Reprod Biol 1996; 67: 133-138.
7 Phibbs R. Hydrops fetalis and other causes of neonatal oedema and ascites. Polin RA, Fox WW. Fetal and Neonatal Physiology. Philadelphia: Saunders, 1992: 1319-1325.
8 Etches PC, Lemons JA. Nonimmune hydrops fetalis: Report of 22 cases including three siblings. Pediatrics 1979; 64: 326-332.
9 Inaba H, Kato K, Ohzawa N, Nakayama K. Effect of urinastatin on disseminated intravascular coagulation (in Japanese). Folia Pharmacol Japon 1986; 88: 239-244.
10 Yoshikawa T, Murakami M, Seto O et al. Protective effects of a protease inhibitor, ulinastatin, on endotoxin shock and its scavenging effect on oxygen-derived free radicals (in Japanese). Jpn J Anesthesiol 1988; 37: 969-974.
11 Endo S, Inada K, Taki K, Hoshi S, Yoshida M. Inhibitory effects of ulinastatin on the production of cytokines: implications for the prevention of septicaemic shock. Clin Ther 1990; 12: 323-326.
12 Ogawa M, Nishibe S, Mori T, Neumann S. Effect of human urinary trypsin inhibitor on granulocyte elastase activity. Res Commun Chem Pathol Pharmacol 1987; 55: 271-274.
13 Nakano M, Yamada S, Hayashi Y et al. Preventive effects of ulinastatin for coronary artery aneurism formation in Kawasaki disease. In: Kato H, ed. Kawasaki Disease: Proceedings of the 5th International Kawasaki Disease Symposium. Tokyo: Elsevier; 1995: 364-371.
14 Iino M, Shiraishi H, Igarashi H, Honma Y, Momoi M. Case of Kawasaki disease in NICU. Pediatr Int 2003; 45: 580-583.
15 Maradny EE, Kanayama N, Halim A, Maehara K, Terao T. Urinary trypsin inhibitor has a protective effect on the amnion. Gynecol Obstet Invest 1994; 38: 169-172.

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