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Case report

Liposteroid and methylprednisolone combination therapy for a case of idiopathic lung hemosiderosis

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ABSTRACT

Idiopathic pulmonary hemosiderosis (IPH) is a rare disease in children, with unknown etiology. The classical clinical triad is hemoptysis, hypochromic anemia and diffuse parenchymal infiltrations on chest X-ray. Liposteroid dexamethasone palmitate, which was developed in Japan, has shown good efficacy for IPH. We present the case of a patient with IPH, who suffered from a life-threatening respiratory dysfunction, and was rescued by a trial administration of liposteroid with methylprednisolone (mPSL).

A 6-year-old girl was admitted to our hospital for repeated dyspnea and blood-stained sputum. She was diagnosed with IPH at the age of three-months by iron staining of gastric fluid and sputum studies. Her cumulative dose of steroids (equivalent to prednisolone (PSL)) was 1062 mg/kg. However, she could not achieve remission. We decided to initiate liposteroid therapy. We administered an infusion of liposteroid 0.8 mg/kg intravenously, for three consecutive days as a therapy for acute bleeding. After administration of liposteroid, she developed high fever with CRP elevation. We suspected that the inflammation was caused by palmitate, which is present as a lipo base in liposteroid. Hence, we added 2 mg/kg mPSL per day for 1 week. As a maintenance treatment, a single infusion of liposteroid was administered followed by mPSL administration for 6 days in every week. Her respiratory condition slowly improved. Tracheostomy was performed for airway management. She was shifted out of the ICU on the 34th day.

Steroid is a key therapy for hemosiderosis. When IPH is diagnosed, oral prednisone therapy is initiated. Although this is effective, there are limitations due to significant adverse effects. Maintaining drug therapy is very important for IPH patients to keep the disease under control. Liposteroid has the same mechanism of action as dexamethasone. It has a Lipo-base, palmitate, which could induce pro-inflammatory cytokine activation. We used mPSL to inhibit the inflammation following liposteroid administration. This was effective. A combination of liposteroid and mPSL administration was useful method of treatment for the patient.

1. Introduction

Idiopathic pulmonary hemosiderosis (IPH) is a rare disease in children, with unknown etiology [1,2]. It is pathologically characterized by recurrent intra-alveolar pulmonary hemorrhage. The patients exhibit symptoms such as dyspnea, cough, and blood-stained sputum. The classical clinical triad is hemoptysis, hypochromic anemia, and diffuse parenchymal infiltrations on chest X-ray. The clinical course can progress aggressively, with death in several cases. Liposteroid dexamethasone palmitate is known for the treatment of rheumatoid arthritis. This drug, which was developed in Japan, is a lipid emulsion containing dexamethasone [3–5].

This drug has shown good efficacy for some immunological diseases such as hemophagocytic syndrome, graft-versus-host disease, and pulmonary hemosiderosis. This efficacy is due to easy uptake of the drug by phagocytes and retention of the drug in macrophages. Doi et al. reported the long-term outcomes of liposteroid in nine children with IPH. Almost all patients showed long remission and normal level of KL6 [6].

We present the case of a patient with pulmonary hemosiderosis, who suffered from a life-threatening respiratory dysfunction, and was rescued by a trial administration of liposteroid.

2. Case presentation

A 6-year-old girl was admitted to our hospital for repeated dyspnea and hemoptysis, with a low oxygen-saturation of 91% in ambient air. She showed labored breathing. On admission, her SpO_2 was 94% with 6 L/min oxygen from a reservoir mask. Computed tomography of chest showed infiltrative shadow in the lower field of both lungs (Fig. 1).

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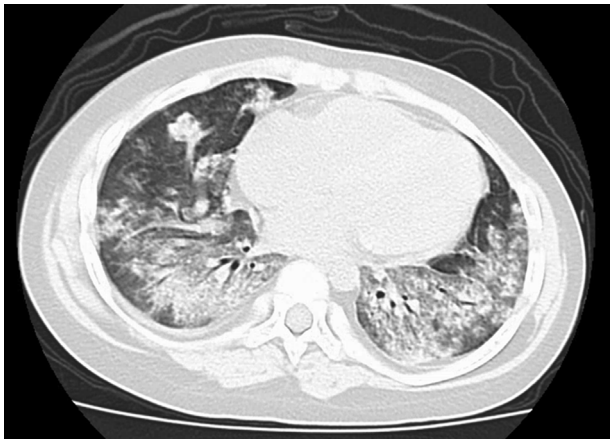

Fig. 1. Computed tomography of chest showed an infiltrative shadow in the lower field of both lungs.

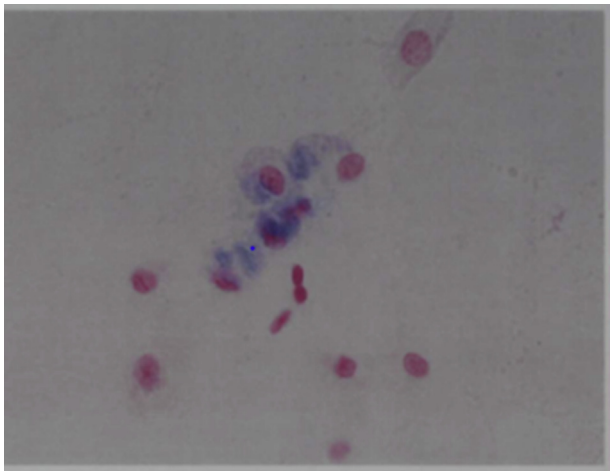

Fig. 2. Pathological findings of gastric fluid showed phagocytosis of hemosiderin.

When she was 3 months old, she was admitted to our hospital with repeated cough and hemoptysis. Her chest X-ray showed ground glass opacity. Hypochromic anemia was also observed. When she was 10 months old, she was diagnosed with IPH based on the results of iron staining of gastric fluid and sputum studies (Fig. 2). Oral or intravenous steroids were administered to the patient several times, but her respiratory condition did not improve. The cumulative dose of steroids (equivalent to prednisolone [PSL]) administered to her was 1062 mg/kg.

During the most recent admission, intravenous corticosteroid was administered in addition to the usual treatment (oxygen, bronchodilators, and steroid inhaler). However, her respiratory condition worsened despite a high dose of dexamethasone equivalent to a pulse dose of methylprednisolone (mPSL) for 3 days. We decided to initiate liposteroid therapy, which has shown good prognosis over long-term use in patients with IPH [6]. After informed consent and approval of the ethics committee, we administered an infusion of liposteroid 0.8 mg/kg intravenously, for three consecutive days as a therapy for acute bleeding in accordance with the protocol reported by Doi et al. [6]. On the second day of liposteroid therapy, she displayed restlessness and irritability, which was considered an adverse effect of the drug. Her respiratory condition worsened and it was difficult to maintain an SpO_2 of > 90%, even with 10 L/min oxygen. Her blood pressure was 180/100 mmHg. Posterior reversible encephalopathy (PRES) syndrome due to adverse effect of liposteroid was suspected. Mechanical ventilation was initiated in the ICU. We provided mechanical ventilation in airway

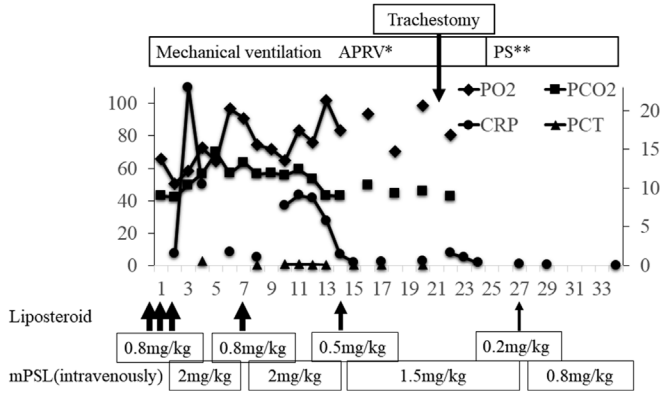

Fig. 3. Clinical course in the ICU. Liposteroid was administered for three consecutive days followed by mPSL administration. The dosage of liposteroid and mPSL was changed according to the data or the patient's condition. *APRV: airway pressure release ventilation; **PS: pressure support.

pressure release ventilation (APRV) mode, to allow spontaneous respiration. Liposteroid was administered on the third day with continuous infusion of sedative drugs. Her clinical course in the ICU is shown in Fig. 3. After administration of liposteroid for 3 days, she developed high fever with CRP elevation (22.99 g/dL). Antibiotics and gamma globulin were initiated for suspected severe bacterial infection, though her vital signs were stable and procalcitonin was not significantly elevated (0.62 ng/mL). We also suspected that the inflammation was caused by palmitate, which is present as a lipo-base in lipoprotein dexamethasone. Hence, we added 2 mg/kg mPSL per day for 4 days. A single infusion of liposteroid was administered 1 week after the first therapy, as maintenance treatment. During the first single infusion of maintenance therapy, we reduced the dose to 0.5 mg/kg, to prevent the adverse effect; however, she complained of pruritus. We decreased the dosage to 0.2 mg/kg during the second week of single infusion. After liposteroid infusion, we administered 0.8–2 mg/kg mPSL for 6 days every week. Her respiratory condition improved slowly. Tracheostomy was performed for airway management on the 21st day in the ICU. She was shifted out of the ICU on the 34th day and was discharged from the hospital 5 months after initiation of liposteroid therapy.

3. Discussion

Patients with lung hemosiderosis show symptoms such as asthma, severe cough, wheezing, and dyspnea in addition to iron-deficiency anemia. Maintenance therapy such as bronchodilator, inhaler and/or oral steroid administration is necessary even if the patient is in a good clinical condition with few symptoms. Hemosiderosis can recur over the years. Physicians should closely observe the patients at fixed intervals and ensure good compliance of medicine. Steroid is a key therapy for hemosiderosis. When IPH is diagnosed, oral prednisone therapy is initiated. Although this is effective, there are limitations due to significant adverse effects. The adverse effects of steroid administration are sometimes aggravated in a child on long-term therapy. The adverse effect can cause growth retardation, osteoporosis, fatty liver, hypertrichosis, etc. Maintaining drug therapy is very important for IPH patients to keep the disease under control. Liposteroid has the same mechanism of action as dexamethasone. However, it has a lipo-base, palmitate, which is saturated fatty acid. Saturated fatty acid is more deleterious to the non-adipose tissue than unsaturated fatty acid [7]. Kim et al. reported that palmitate strongly induced apoptosis of macrophages, which can lead to endoplasmic reticulum stress and cause proliferation of reactive oxygen species [7]. This palmitate-induced lipotoxicity to the macrophages, might be beneficial for immune-mediated conditions, in addition to high transferability and retention in the

target tissues [8,9]. Wang et al. reported that palmitate induced NLRP3 inflammasome activation leads to caspase-1 activation, which induces pyroptosis [9]. Caspase 1 induces pro-inflammatory cytokine activation such as interleukin-1 (IL1) and interleukin-18 (IL18). This mechanism could be the reason for CRP elevation and high fever after administration of liposteroid in our case [10,11]. The initial dose might have been too high, leading to CRP elevation and high fever, in addition to mental instability in the patient. We decided the dose of liposteroid based on the protocol reported by Doi et al. [6]. Liposteroid was administered to the patient in May 2015. However, an erratum for that article was issued in September 2015, and the dose of liposteroid was corrected to 10% of the original dose [12]. Moreover, since the patient had gained weight due to long-term steroid administration, the dose calculation should have been done using lean body mass. We used mPSL to inhibit the inflammation following liposteroid administration. As a result, the dose of liposteroid (0.2 mg/kg) did not have any adverse effect following mPSL administration. Although the dose was higher than the corrected dose of liposteroid [12], it could be considered an appropriate dose if followed by mPSL administration.

The combination of liposteroid and mPSL administration was a useful method for the treatment of our patient.

4. Conclusions

Liposteroid administration is effective for a steroid resistant IPH patient. It is necessary to calculate the dose accurately and watch for adverse effects after initial administration. Combination with mPSL was effective probably due to the inhibition of inflammatory response caused by liposteroid, in addition to the inhibition of IPH progression.

Financial disclosure

None of the authors has any conflicts of interest with the contents.

Proprietary statement

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Declarations of interest

None.

References

[1] T.G. Nuesslein, N. Teig, C.H.L. Rieger, Pulmonary haemosiderosis in infants and children, Paediatr. Respir. Rev. 7 (2006) 45–48.
[2] O.C. Ioachimescu, S. Sieber, A. Kotch, Idiopathic pulmonary haemosiderosis revisited, Eur. Respir. J. 24 (2004) 162–170.
[3] H. Wakiguchi, S. Ohga, Clinical utility of the liposteroid therapy: potential effects on the macrophage activation, Jpn. J. Clin. Immunol. 39 (2016) 190–196.
[4] Y. Mizushima, T. Hamano, K. Yokoyama, Tissue distribution and anti-inflammatory activity of corticosteroids incorporated in lipid emulsion, Ann. Rheum. Dis. 41 (1982) 263–267.
[5] S.H. Mullewr, J.H. Diaz, A.D. Kaye, Clinical applications of intravenous lipid emulsion therapy, J. Anesth. 29 (2015) 920–926.
[6] T. Doi, S. Ohga, M. Ishimura, et al., Long-term liposteroid therapy for idiopathic pulmonary hemosiderosis, Eur. J. Pediatr. 172 (2013) 1475–1481.
[7] D.H. Kim, Y.M. Cho, K.H. Lee, S.W. Jeong, O.J. Kwon, Oleate protects macrophages from palmitate-induced apoptosis through the downregulation of CD36 expression, Biochem. Biophys. Res. Commun. 488 (2017) 477–482.
[8] E. Lee, J. Choi, H.S. Lee, Palmitate induces mitochondrial superoxide generation and activates AMPK in podocytes, J. Cell. Physiol. 232 (2017) 3209–3217.
[9] L. Wang, Y. Chen, X. Li, Y. Zhang, E. Gulbins, Y. Zhang, Enhancement of endothelial permeability by free fatty acid through lysosomal cathepsin B-mediated Nlrp3 inflammasome activation, Oncotarget 7 (2016) 73229–73241.
[10] G. Doitsh, N.L. Galloway, X. Geng, et al., Cell death by pyroptosis drives CD4 T-cell depletion in HIV-1 infection, Nature 505 (2014) 509–514.
[11] I. Jorgensen, E.A. Miao, Pyroptotic cell death defends against intracellular pathogens, Immunol. Rev. 265 (2015) 130–142.
[12] T. Doi, S. Ohga, M. Ishimura, et al., Erratum to: long-term liposteroid therapy for idiopathic pulmonary hemosiderosis, Eur. J. Pediatr. 174 (2015) 1701.