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Liposteroid against refractory pulmonary haemorrhage in idiopathic pulmonary haemosiderosis

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Abstract We describe two Japanese children with idiopathic pulmonary haemosiderosis (IPH), whose refractory haemorrhages were treated with an intravenous lipid emulsion containing dexamethasone (liposteroid). A 22-month-old boy and a 14-month-old girl have been observed with similar symptoms; periodic bouts of anaemia, reticulocytosis, diffuse infiltrates on chest X-ray and the finding of siderophages in sputum or gastric lavage fluid. The MRI of the lung was useful for the diagnosis. Methylprednisolone pulse therapy was successful in treating acute massive bleeding. Subsequent oral prednisolone could not prevent chronic recurrent haemorrhages. However, the intermittent administration of liposteroid (0.05 mg/kg/dose IV) led to a cessation of bleeding; the haemoglobin concentration rose to normal levels. This observation emphasizes the usefulness of liposteroid in the management of refractory IPH.

Key words Idiopathic pulmonary haemosiderosis · Liposteroid Methylprednisolone · Magnetic resonance imaging

Abbreviations *IDA* iron deficiency anaemia · *IPH* idiopathic pulmonary haemosiderosis · *mPSL* methylprednisolone · *UIBC* unsaturated iron binding capacity

Introduction

Idiopathic pulmonary haemosiderosis (IPH) is a rare disorder of children characterized by recurrent pulmonary haemorrhage with the accumulation of haemosiderin in lung tissues [8, 9, 11]. Its rarity and clinical manifestations make it difficult to differentiate from iron deficiency anaemia (IDA) or haemolytic anaemia. About 50% of these patients die within a few years from acute pulmonary haemorrhage or from progressive respiratory failure due to chronic bleeding [8, 11]. However, there is little information on the pathophysiology and effective treatment for this disease.

We present two children with IPH with emphasis on the diagnostic problems and the favourable response to liposteroid: lipid emulsion containing dexamethasone, which appears to present a new option for managing IPH.

Case report

Case 1

This 22-month-old Japanese boy was first diagnosed as having haemolytic crisis and pneumonia on October 15, 1992. There was rhinorrhoae, cough, fever and an infiltrate in the right lung on chest X-ray. Pallor and low grade fever had been present for about 1 month. Because of the progressive anaemia and tachypnoea, he was referred to our hospital on 20 October 1992. He had been born to a healthy mother at 26 weeks of gestation, and weighted 974 g upon vaginal delivery. Mechanical ventilation was required for 3 days to manage neonatal respiratory distress, but there were no cardiopulmonary sequelae. His neurological development was consistent with his chronological age. There was no family history of lung disease or immunohaematological disorders.

On admission, physical examination revealed a body temperature of 37.6° C, pulse rate of 144/min and a respiration rate of 66/min. He was a pale dyspnoeic boy with a scaphoid head, puffy face and mild icterus. The liver was palpated 3 cm below the costal margin, and the tip of the spleen was palpable. Auscultation re-

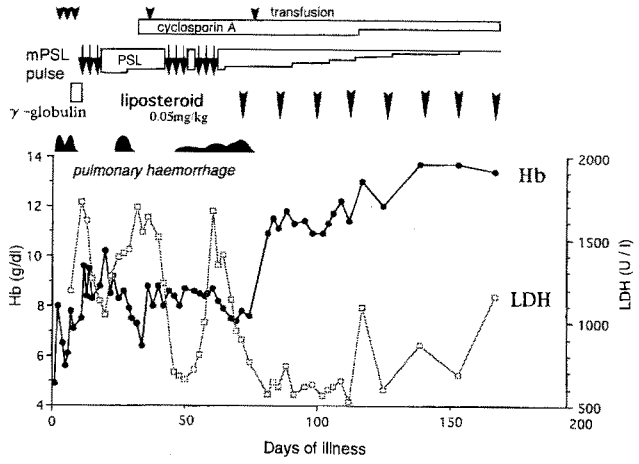

Fig. 1 Clinical course of Case 1. Blood transfusion and mPSL pulse therapy, 30 mg/kg daily for 3 days was effective in relieving a haemorrhagic symptoms. However, the administration of PSL and cyclosporin failed to reduce the episodes of chronic recurrent bleeding. The intravenous administration of a liposteroid (Limethasone Green Cross Company, Osaka, Japan) at a dose of 0.05 mg/kg every 2 weeks led a marked remission of haemorrhage with an improvement in Hb concentration

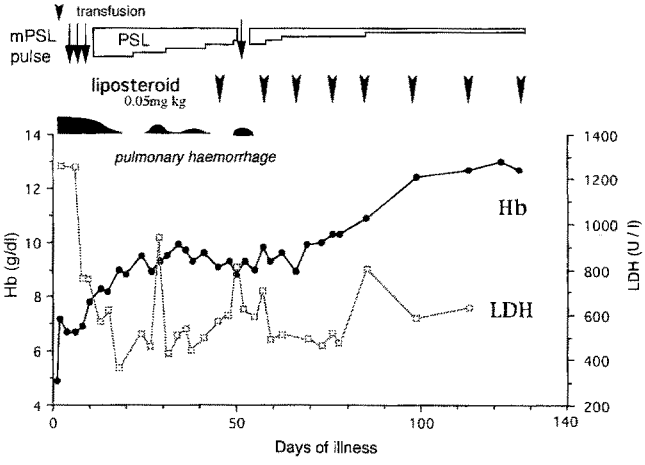

Fig. 2 Clinical course of Case 2. Blood transfusion and mPSL pulse therapy were effective in treating the acute haemorrhagic symptoms. However, subsequent treatment with oral PSL did not reduce the haemorrhagic attacks. The liposteroid therapy prevented chronic bleeding leading to an elevation of Hb concentration

vealed fine moist râles in the right lung. There was strabismus related to retinopathy of prematurity.

Laboratory studies (16 October 1992, the 1st day in Fig. 1) revealed WBC 14.15 × 10^9/l, RBC 2440 × 10^9/l, Hb 6.1 g/dl, platelets 37.4 × 10^9/l and a reticulocyte count of 12.7%, indicative of normocytic hypochromic anaemia. Blood chemistry showed AST 66 IU/l (normal range. n = 7–33), ALT 6 IU/l (n = 5–30), LDH 1,655 IU/l (n:260–480), total bilirubin 3.1 mg/dl, and direct bilirubin 0.8 mg/dl. Serum iron and ferritin levels were decreased to 31 μg/dl (n = 70–190) and 45.5 ng/ml (n = 25–250), respectively, while the unsaturated iron binding capacity (UIBC) was 333 μg/ml (n = 130–370). Serum levels of haptoglobin and haemopexin were decreased to 8 mg/dl (n = 45–320) and 35 mg/dl (n = 50–115), respectively. C-reactive protein level was 0.2 mg/dl. Serological studies demonstrated no primary virus infections. The Coombs test was negative. Tests for immune complex and antiglomerular basement membrane antibody were negative. No specific antibodies to milk protein were detected. Serum Ig levels showed IgG 1,024 mg/dl, IgA 84 mg/dl and IgM 102 mg/dl. Natural killer activity was depressed to 5.6% lysis (control range: 20.8–40.8), while mitogen response and surface marker analysis of lymphocytes were normal. Chest X-ray showed bilateral diffuse infiltration and scattered micronodular shadows. Sputum cytology demonstrated numerous macrophages laden with haemosiderin on Prussian blue staining. MRI of the lung on day 23 of the illness revealed diffuse low intensity on T_2-weighted image, which inversely showed high intenstiy on T_1-weighted image, suggesting the accumulation of haemosiderin. Sequential changes in histogram of Hb concentration illustrated no predominant decrease of his hypochromic red cells to transfused normochromic red cells during each anaemic attack, indicating the blood loss but not immune haemolysis. These findings confirmed the diagnosis of IPH. Lung biopsy was not performed.

High dose γ-globulin therapy was ineffective (Fig. 1). Blood transfusions and methylprednisolone (mPSL) pulse therapy, 30 mg/kg daily for 3 days, ameliorated the haemorrhagic symptoms. The oral administration of prednisolone (2 mg/kg) and cyclosporin (5 mg/kg) failed to control the bleeding, while liposteroid (Limethasone, Green Cross Company, Osaka, Japan), 0.05 mg/kg infused intravenously every 2 weeks, led to a remission. Few siderophage was detected in the gastric fluids. Hb concentration, serum iron, UIBC and ferritin levels promptly normalized and remained at these levels for 14 months, although only a haemorrhagic attack occurred following one time discontinuance of liposteroid due to a bacterial infection.

Case 2

This 14-month-old Japanese girl was referred to us under a tentative diagnosis of haemolytic anaemia on 19 May 1992. Studies of red cell enzymes and globin chain were normal. She received blood transfusion for a suspected haemolytic crises on 26 November (Hb 5.4 g/dl) and again on 6 December (Hb 5.2 g/dl). On 16 December, she was hospitalized with pallor, fatigue and bloody rhinorrhoea. The child had been a full-term and normal delivery. Her mother suffered from ulcerative colitis, but there were no immunohaematological disease in the family.

On admission, her body temperature was 37.5°C, pulse rate was 144/min and the respiratory rate was 78/min. Physical examination revealed a pale listless girl. Liver was palpable 1 cm below the costal margin, and spleen was not palpable. Respiratory sounds were decreased over the right lung with no rales.

Laboratory studies (16 December 1992, the 1st day in Fig. 2) revealed WBC 8.40 × 10^9/l, RBC 2210 × 10^9/l, Hb 4.9 g/dl, platelets 39.4 × 10^9/l and a reticulocyte count of 5.6%, indicating normocytic hypochromic anaemia. Blood chemistry showed AST 46 IU/l, ALT 8 IU/l, LDH 1,256 IU/l, total bilirubin 1.7 mg/dl and direct bilirubin 0.3 mg/dl. Serum levels of iron and ferritin were decreased to 19 μg/dl and 45.5 ng/ml, respectively, while the UIBC was 264 μg/dl. Serum haptoglobin was not detectable. C-reactive protein was less than 0.2 mg/dl. Serological examination revealed no primary virus infections. Immune complex, and specific antibodies to anti-glomerular basement membrane or milk protein were not detected. Serum Ig levels showed IgG 668 mg/dl, IgA 71 mg/dl and IgM 149 mg/dl. Natural killer activity was depressed to 3.9% lysis (control range: 8.9–29.5), while mitogen response and surface marker analysis of lymphocytes were normal. Chest X-ray showed diffuse infiltrates in the right lung. Cytology of gastric lavage fluid demonstrated numerous siderophages. MRI findings

were indicative of haemosiderin accumulation during a relapse, but not at the initial diagnosis. Sequential changes in Hb histogram resembled those of Case 1. These findings led to a diagnosis of IPH. No lung biopsy was done.

She was treated with blood transfusion and mPSL pulse therapy during the acute massive bleeding (Fig. 2). Except for only one attack, subsequent haemorrhage were prevented by the liposteroid therapy (0.05 mg/kg every 10–14 days). The siderophages disappeared in her gastric fluid. However, she suffered a relapse of chronic haemorrhage after a remission of 4 months. Oral cyclophosphamide was ineffective. The liposteroid therapy, oral azathioprine (1 mg/kg, daily), and an inhalation of flunisolide (25 μg/dose 5 times a day) have now well controlled the pulmonary haemorrhage.

Discussion

The present cases illustrate the potential effectiveness of lipsteroid in treating recurrent pulmonary haemorrhages, although the follow up time was relatively short. Liposteroid is the dexamethasone palmitate ester incorporated in liposome, which is developed as a drug carrier vehicle for appropirate distribution to the target site and decreasing systemic side-effects [13, 21]. Bonanomi et al. [3] showed the long retention of liposteroid in synovial fluid and no suppression of the endogenous cortisol levels in rabbit models. Hoshi et al. [6] revealed that this agent had a higher improvement rate of rheumatoid arthritis and lower frequency of side-effects than dexamethasone. Since the liposteroid reaches the local inflamed sites [3, 13], its effect might depend on the concentration of corticosteroid in IPH lung tissues. Furthermore this agent could inhibit the activation of pulmonary macrophages [13] to accumulate the haemosiderin in the lung. Little is known about the pathogenesis of IPH, however, a variety of immune disorders [2, 7, 15, 17, 20] in IPH patients and an appreciable response to immunosuppressive agents [4, 9] are suggestive of an immunopathological basis. Of interest, both patients showed depressed NK activity in concordance with the previous reports [12], although this pathognomonic significance was obscure. While IPH partly tends to have a remitting nature, the timing of the clinical improvement observed here strongly suggests a favourable response to liposteroid.

Another concern is the diagnostic problems of IPH, because this rare disorder shares features of IDA and haemolytic anaemia. Guttenberg et al. [5] described only five cases in Scandinavia during a period of 23 years. Kjellman's 30-year survey [8] disclosed only 10 Swedish children with IPH. Records at our hospital, a tertiary centre for 20 years, revealed only three cases, two of which are presented here. The third patient was a 10-year-old girl who died of massive pulmonary haemorrhage following treatment for 6 years with oral PSL. Patients with IPH rarely present with haemoptysis [1, 8]. All three cases showed hypochromic anaemia without notable pulmonary symptoms from the beginning. The detection of siderophages [16] and/or the characteristic MR images (low intensity on T_2- and high on T_1-weighted images) [18] favoured the diagnosis of pulmonary haemosiderosis. Although a lung biopsy is required to confirm the diagnosis [19], careful clinical observation and new radiological techniques [10, 14, 18] can be useful for the correct diagnosis. This report sheds some light on the diagnosis and treatment of IPH; a new regimen for managing refractory IPH consisting of the administration of mPSL for the acute haemorrhage, and of liposteroid to prevent chronic recurrent bleeding.

References

1. Aledort LM, Lord GP (1967) Idiopathic pulmonary hemosiderosis. sever anemia without hemoptysis- one year follow-up of pulmonary function. Arch Intern Med 120:220–223
2. Bain SC, Bryan RL, Hawkins JB (1989) Idiopathic pulmonary haemosiderosis and autoimmune thyrotoxicosis. Respiratory Med 83: 447–450
3. Bonanomi MH, Velvart M, Stimpel M, Roos KM, Fehr K, Weder HG (1987) Studies of pharmacokinetics and therapeutic effects of glucocorticoids entrapped in liposomes after intraarticular application in healthy rabbits with antigen-induced arthritis. Rheumatology 7: 203–212
4. Colombo JL, Stolz SM (1992) Treatment of life-threatening primary pulmonary hemosiderosis with cyclophosphamide. Chest 102:959–960
5. Guttenberg TJ, Moe PJ, Noren CE (1979) Diagnosis and therapeutic studies in idiopathic pulmonary hemosiderosis. Acta Paediatr Scand 68: 913–914
6. Hoshi K, Mizushima Y, Shiokawa Y, Kageyama T, Honma M, Kashiwazaki S, Shichikawa K, Tsunematsu T, Kaneko K (1985) Double-blind study with liposteroid in rheumatoid arthritis. Drug Exptl Clin Res XI (9):621–626
7. Katz SM, Foster E, Miller AS, Krevolin L, Schwaqrtz AB (1989) Goodpasture's syndrome mimicking idiopathic pulmonary hemosiderosis. Ann Clin Lab Sci 19:280–286
8. Kjellman B, Elinder G, Garwicz S, Svan H (1984) Idiopathic pulmonary hemosiderosis in Swedish children. Acta Paediatr Scand 73:584–588
9. Levy J, Wilmott RW (1986) Pulmonary hemosiderosis. Pediatr Pulmonol 2:384–391
10. Lynch DA, Brasch RC, Hardy KA, Webb WR (1990) Pediatric pulmonary disease: assessment with high-resolution ultrafast CT. Radiology 176: 243–248
11. Matsaniotis N, Karpouzas J, Apostolopoulou E, Messaritakis (1968) Idiopathic pulmonary hemosiderosis in children. Arch Dis Child 43:307–309
12. Mayumi S, Junji T, Masaru K, Toshio T, Kenzo F (1987) A case of idiopathic pulmonary hemosiderosis with depressed natural killer activity. Jpn J Pediatr (Shounika Rinshou) 40: 2287–2291
13. Mizushima Y, Hamano T, Yokoyama K (1982) Tissue distribution and anti-inflammatory activity of corticosteroids incorporated in lipid emulsion. Ann Rheumatic Dis 41:263–267
14. Muller NL, Miller RR (1991) Diffuse pulmonary hemorrhage. Radiol Clin North Am 29:965–971

15. O'Donohue WJ Jr (1974) Idiopathic pulmonary hemosiderosis with manifestations of multiple connective tissue and immune disorders. treatment with cyclophosphamide. Am Rev Respir Dis 109:473–479
16. Perez-Arellano JL, Garcia J-E L, Macias MCG, Gomez FG, Lopez AJ, Castro S de (1992) Hemosiderin-laden macrophages in bronchoalveolar lavage fluid. Acta Cytol 36:26–30
17. Rafferty JR, Cook MK (1984) Idiopathic pulmonary haemosiderosis with autoimmune haemolytic anemia. Br J Dis Chest 78:282–285
18. Rubin GD, Edwards DKIII, Reicher MA, Doemeny JM, Carson SH (1989) Diagnosis of pulmonary hemosiderosis by MR imaging. AJR 152:573–574
19. Travis WD, Colby TV, Lombard C, Carpenter HA (1990) A clinicopathologic study of 34 cases of diffuse pulmonary hermorrhage with lung biopsy confirmation. Am J Sur Pathol 14: 1112–1125
20. Williams S, Craver RD (1989) Cow's milk-induced pulmonary hemosiderosis. J Louisiana State Med Soc 141: 19–22
21. Yokoyama K, Okamoto H, Watanabe M, Suyama T, Mizushima Y (1985) Development of a corticosteroid incorporated in lipid microspheres (liposteroid). Drug Exptl Clin Res XI(9): 611–620