ACUTE IDIOPATHIC PULMONARY HEMORRHAGE IN INFANTS. REPORT OF TWO CASES AND LITERATURE REVIEW

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ABSTRACT

Acute idiopathic pulmonary hemorrhage is a rare life-threatening disease in children. The classic triad includes hemoptysis, anemia and respiratory distress. Since clinical presentation may vary, diagnosis can be difficult. Severe respiratory distress, and ventilatory failure requiring mechanical ventilation are often present. Chest X-rays usually show unilateral or bilateral infiltrates, therefore, other causes of pulmonary hemorrhage must be excluded, since most of them correspond to systemic diseases. Treatment often requires intravenous steroids to solve the respiratory failure in most cases.

We present two cases involving infants treated at Hospital San José (a fourth level hospital in Bogotá, Colombia) with acute idiopathic pulmonary hemorrhage which required mechanical ventilation and responded to intravenous steroids. A literature review was conducted with special emphasis on clinical presentation, diagnosis and therapeutic approaches.

INTRODUCTION

Diffuse pulmonary hemorrhage is a rare disease in the pediatric population, originated in the pulmonary microvasculature and, in most cases, associated with systemic diseases. When presented in isolation and possible systemic causes are discarded, it is known as idiopathic pulmonary hemosiderosis or idiopathic pulmonary hemorrhage (IPH) (1).

According to the American Center for Disease Control (CDC), acute idiopathic pulmonary hemorrhage (AIPH) refers to a pulmonary hemorrhage episode in a previously healthy infant with no history nor other neonatal diseases that may be considered as the cause. AIPH is manifested as hemoptysis, epistaxis or bleeding in the airway, unrelated to bleeding in the upper respiratory tract or digestive tract. It must be associated with severe respiratory distress or ventilatory failure, and mechanical ventilation is also required; chest X-ray or CT should show unilateral or bilateral alveolar infiltrates (2). Data on incidence is scarce, and most information comes from case reports: the largest American series has 47 cases (3), followed by Japan with 39 cases (4), France with 25 and Sweden with 19 (5,6). On the other hand, there are no pediatric case reports in Colombia.

Two cases of previously healthy infants who developed AIPH, respiratory failure and required mechanical ventilation are presented. These cases were treated at the Pediatric Intensive Care Unit (PICU) at Hospital San José (HSJ), a fourth-level university hospital in Bogotá, Colombia, which also provided the necessary data from clinical charts. For the first case, consent was requested, and follow-up was done; in the second case, the patient could not be located for follow-up. Furthermore, a review of existing clinical literature was used to conclude that early diagnosis of this disease, which is life-threatening, allows an adequate therapeutic approach, which may reduce morbidity and mortality.

PRESENTATION OF THE CASES

Case 1

Male, 40-days-old patient from Bogotá, born at full term, with normal neonatal adaptation, and appropriate weight and size. He was admitted to the emergency room due to a

sudden onset of heavy nose and oral cavity bleeding, associated with marked pallor and loss of tone. He presented cardiorespiratory arrest, so resuscitation was performed for 10 minutes and tracheal intubation showed heavy bleeding. Conventional mechanical ventilation and inotropic support with epinephrine was initiated; after stabilization, he was transferred to the PICU.

Important history included pentavalent, pneumococcal, rotavirus and oral polio vaccination the same day in the morning, and a feverish peak was treated with acetaminophen. This was reported to Instituto Nacional de Salud (local government health institution), who, after a case review concluded that the clinical picture could not be related to vaccination, since no similar cases were found in the literature. Exposure to tobacco smoke was discarded, the residence site had drinking water and no outstanding humidity was reported. Additionally, family history was uneventful and physical examination findings showed no other bleeding sites nor signs of abuse.

Central venous blood gases showed anemia with hemoglobin of 7.7 g/dl; clotting times were prolonged, and partial thromboplastin time was 55.4s with control time 30.1s. Prothrombin time was 13.6s with control time 10.9s and fibrinogen was 530 mg/dl. Renal function and aminotransferases were normal, C-reactive protein was negative, electrolytes were normal, transfontanelar ultrasound was normal and chest x-ray showed alveolar opacities in patches in all four quadrants.

The patient was diagnosed with idiopathic pulmonary hemorrhage and severe anemia that required transfusion of packed red blood cells at a dose of 20 ml/kg; methylprednisolone 1 mg/kg was also administered intravenously every 6 hours. The patient improved, inotropic support was discontinued, ventilatory parameters were decreased and was extubated on the third day. The hemogram performed after transfusion was normal, showing leukocytes 9800cel/µl, neutrophils 7800cel/µl, monocytes 700cel/µl, lymphocytes 1800cel/µl, hemoglobin 12.5 g/dl, hematocrits 37.1%, MCV 91.4 fl, MCH 30.8 pg, RDW 148% and platelets 238000 cells/µl. During hospital stay, the patient had thrombin time 16.3s and no new bleeding episodes occurred. The slightly altered clotting times were interpreted as caused by a post arrest effect.

Methylprednisolone was administered for four days, followed by prednisolone orally at doses of 1 mg/kg/day, with a gradual dose reduction until discontinuation on day 10. During hospital stay, he developed a urinary tract infection by Citrobacter freundii, an extended-spectrum β-lactamase producing bacteria, associated with the urinary catheter used. Therefore, ertapenem 15 mg/kg/dose was administered every 12 hours for 10 days. The patient was discharged after 17 days of hospitalization with an order for urethrocystography, which was normal. The patient was subsequently evaluated in a follow-up clinic at the age of 39 months; he was found healthy, with a good nutritional condition, normal neurodevelopment status, and no new episodes of bleeding nor heart or lung disease.

Case 2

Nine-weeks-old female patient, from Bogotá, born vaginally, full term, with normal neonatal adaptation, and adequate weight and height for age. The patient was admitted to a sec-

ond-level hospital with a clinical picture of two days of Bristol stool type 1 with blood traces. During observation, she presented mild respiratory distress without other symptoms, so supplemental oxygen was supplied improving oximetry and breathing pattern. She suddenly presented respiratory arrest, and resuscitation and endotracheal intubation was performed, and was then referred to HSJ.

On admission to PICU, the patient was hypoxemic with severe oxygenation disorder, poorly perfused and heavy bleeding was seen during endotracheal intubation. Laryngoscopy showed infra-glottal bleeding; the endotracheal tube was changed and conventional mechanical ventilation with high parameters was used. Physical examination showed no other signs of bleeding nor abuse. An interview with the mother revealed breast and formula feeding, no exposure to tobacco smoke, no abnormal humidity at place of residence, availability of drinking water and no remarkable medical family history.

Laboratory test results showed severe normocytic, heterogeneous normochromic anemia with hemoglobin 6.3 g/dl, hematocrits 19%, mean corpuscular volume 90 fl, mean corpuscular hemoglobin 29.8 pg, mean corpuscular hemoglobin concentration 32.9 g/dl and red cell distribution width 14.1%. In addition, the patient presented leukopenia 1800 cells/ml and neutropenia 700 cells/µl, with normal platelet count, normal clotting time PT 11.5s with control time 10.5, INR 1.09 and PTT 30.5s with control time 30.5, elevated aspartate aminotransferase 179 U/L and alanine aminotransferase 191 U/L, hypoalbuminemia 1.9 g/dL and C-reactive protein 4.1 mg/dL. Chest X-ray showed diffuse alveolar involvement in the four quadrants, without air trapping nor pleural effusion. An echocardiogram was performed with normal results. After analyzing these findings, the diagnosis was: multilobar pneumonia, pulmonary sepsis and possibly, acute idiopathic pulmonary hemorrhage (Figure 1).

To treat this infection, piperacillin/tazobactam 300 mg/kg/intravenous dose was initiated. Due to a distributive shock, vasopressor support with noradrenaline was also initiated, and a packed red blood cells transfusion was given. Because of the torpid evolution and the possibility of idiopathic pulmonary hemorrhage, on the following day, methylprednisolone 1 mg/kg/intravenous dose was ordered every 6 hours. On the second day steroids use, a control X-ray was done. A significant improvement in alveolar involvement was found, requiring a decrease in ventilatory parameters. Vasoactive support was discontinued after completing four days in steroids (Figures 2 and 3).

During hospital stay, no signs of infection was found and both viral panel and blood cultures were negative, so piperacillin/tazobactam was discontinued. Extubation was done at day 5, but reintubation was necessary due to laryngotracheitis associated with mechanical ventilation. Eight days after admission, the patient was finally extubated with success and discharged on oxygen with nasal cannula due to desaturation at room air.

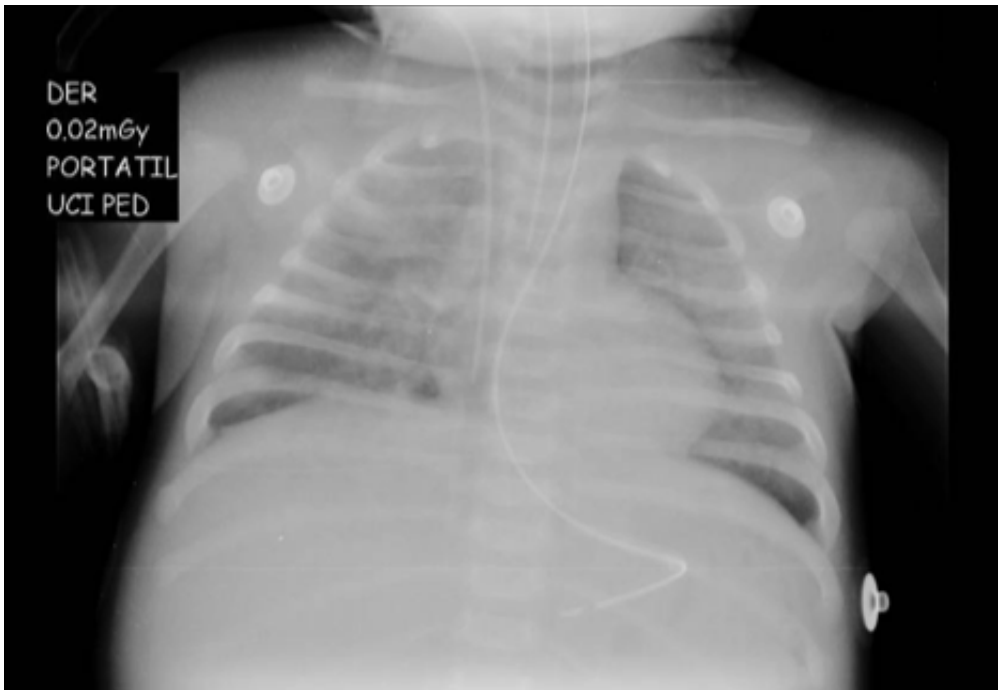

Fig 1. Chest x-ray, diffuse alveolar infiltrates.
Source: Own elaboration based on the data obtained in the study.

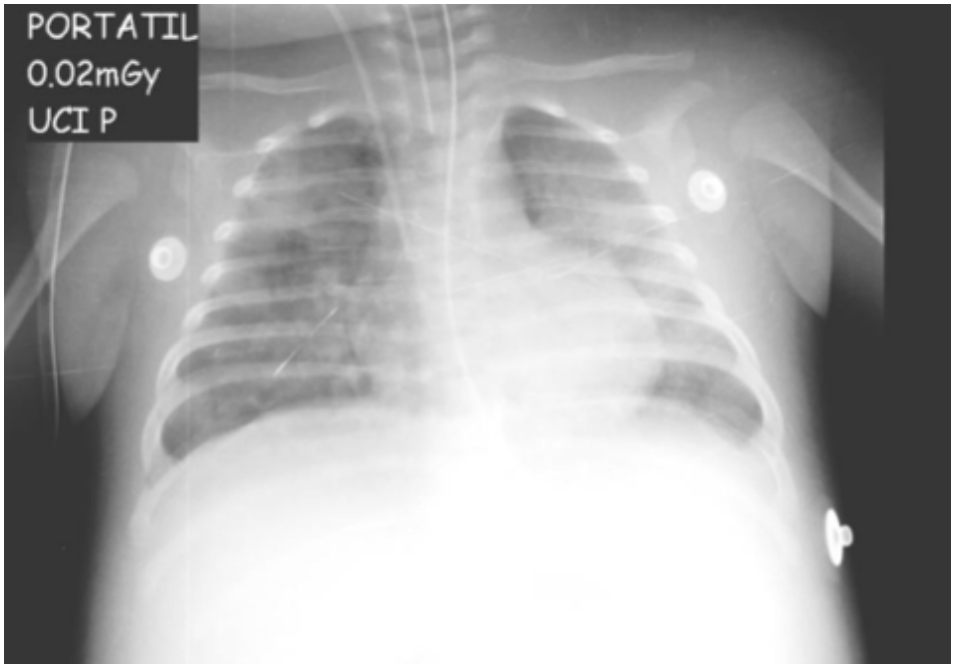

Fig 2. Chest x-ray: improvement in alveolar infiltrates after steroid use (2days).
Source: Own elaboration based on the data obtained in the study..

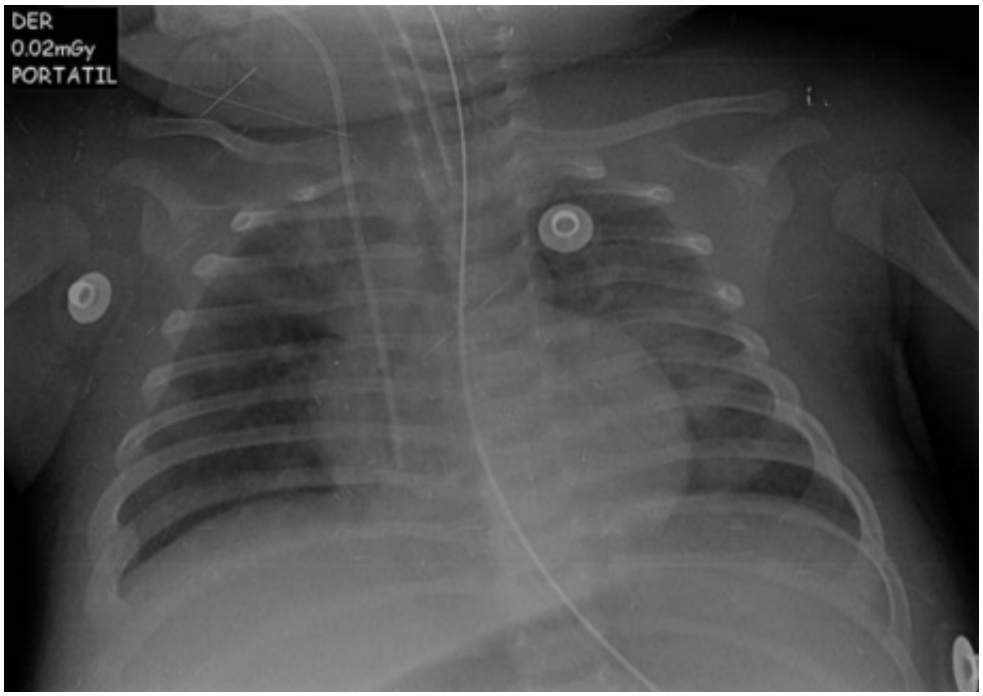

Fig 3. Chest x-ray: improvement in alveolar infiltrates after steroid use (4 days).
Source: Own elaboration based on the data obtained in the study.

DISCUSSION

Frequency

Pulmonary hemorrhage is exceedingly infrequent in children, so IPH is a rare cause of diffuse alveolar hemorrhage in this population. It is seen more often in children under the age of 10, mainly between 1 and 7, and without a clear impact of gender.

In Sweden, between 1950 and 1979, 10 cases were reported, representing an annual risk of 0.24 cases per million children (6). In Japan, for a period of 20 years (1974-1993), 39 cases were documented with an incidence of 1.23 cases/year per one million children (4). In the United States, initially, several outbreaks were reported: between 1992 and 1994, 7 cases of AIPH were documented in Chicago (3); between 1994 and 1997, an outbreak of 10 cases was identified in Cleveland, and, finally, 30 cases treated at Rainbow Babies and Children's Hospital between 1993 and 2000 (7) were reported. In France, 25 cases were reported from 1999 to 2012 (5).

Concepts and classification

Diffuse alveolar hemorrhage may result from immune processes such as vasculitis mediated by neutrophil cytoplasmic antibodies, anti-glomerular basement membrane syndrome, connective tissue diseases, or antiphospholipid syndrome. It could also be due to vasculitis mediated by IgA or cow's milk protein allergy, among others. Moreover, it may also be related to non-immune processes such as infection, heart disease, respiratory distress syndrome or acute coagulopathy. It has also been described as secondary to drugs and

toxics. When all the causes mentioned above have been ruled out, it is possible to diagnose idiopathic pulmonary hemorrhage. (8)

Risk factors and etiology

The IPH etiology is not yet clearly established. During the Cleveland outbreak, some risk factors, such as male sex, lack of breastfeeding, exposure to tobacco smoke and water pollution 6 months prior to the episode were reported. Exposure to fungi, especially to Stachybotrys chartarum toxin, was also suspected. However, CDC decided that establishing a causal relationship between Stachybotrys chartarum and IPH was not possible based on the existing evidence. It is worth considering that exposure to chemical agents has also been involved in other series (7).

Some authors have suggested that risk factors for sudden infant death syndrome (SIDS) may be related to IPH cases, because blood has been found in the airways of infants who died and were diagnosed with SIDS. A study in New Zealand found nosebleed in 15% of cases (9) and another study reported alveolar hemorrhage in 47% of autopsies (10). Nevertheless, pulmonary hemorrhage is common among autopsies in children, especially if cardiopulmonary resuscitation was performed. So it is difficult to conclude whether pulmonary hemorrhage was the cause of death or a marker for some other problem which resulted in death. (11)

Idiopathic pulmonary hemorrhage may be associated with celiac disease and this relationship is known as Lane-Hamilton syndrome. So far, there are few cases reported in the literature and only two theories have been proposed to explain the common pathogenetic pathways. The first suggests the presence of circulating immune complexes acting on the epithelial basement membrane, on the endothelial lung and on the enterocyte; the second proposes that this happens due to inadequate local immune response to T-cells in both entities during gluten intake in genetically predisposed individuals (12). In a cohort of 25 patients with IPH in France, antibodies specific to celiac disease samples were taken in 14 patients (56%), of which four (28%) were positive (5).

Clinic

IPH clinical presentation is characterized by the classic triad of hemoptysis, anemia and infiltrates on chest x-ray due to alveolar bleeding; however, these findings do not always occur simultaneously, which can delay diagnosis. When hemoptysis is severe, it can be life threatening, manifesting itself with breathing difficulty, abdominal pain, hepatosplenomegaly, leukocytosis (13) and bilateral alveolar or interstitial opacities in chest x-ray, which can lead to misdiagnose pneumonia (14).

The patients in this series presented an acute severe respiratory clinical picture; one case with the classic triad that allowed early diagnosis and the other, whose initial diagnosis was pneumonia, with anemia, interstitial opacities on chest x-ray and pulmonary bleeding during laryngoscopy. Moreover, AIPH was proposed for the second case based on torpid evolution of antimicrobial management as described in the literature. Unfortunately, the hospital lacked the necessary equipment to perform bronchoalveolar lavage, which is the ideal next step to complete the study.

Another form of presentation of AIPH is chronic pulmonary hemorrhage, manifested as iron deficiency anemia unresponsive to iron therapy, accompanied with respiratory symptoms such as coughing, wheezing, shortness

of breath, recurrent or chronic cyanosis, along with the appearance of swallowed blood, which can be confused with digestive tract bleeding (13). Recurrent bleeding episodes can cause progressive pulmonary fibrosis, thus, establishing an early treatment is important (5).

Diagnosis

AIPH is an exclusion diagnosis, therefore, in 2004, CDC established the criteria: a case is confirmed only when it occurs in infants younger than 1 year, with a gestational age at birth greater than 32 weeks, without neonatal medical history associated to pulmonary hemorrhage and with the following conditions (2):

1. Sudden onset of hemorrhage or evidence of bleeding in the airway, with signs such as epistaxis, hemoptysis and frank infra-glottic blood unrelated to medical procedures, or identification of more than 20% of hemosiderin-laden macrophages in bronchoalveolar lavage or biopsy. It is necessary to discard oropharynx and nasal bleeding.
2. Severe disease that leads to acute respiratory distress or respiratory failure, which should lead to hospitalization in a PICU or in a neonatal intensive care unit with intubation and mechanical ventilation.
3. Unilateral or bilateral diffuse pulmonary infiltrates on chest x-ray or chest CT documented in the first 48 hours of valuation.

For diagnosis of AIPH, physical abuse, disease with lung involvement at birth, history of bronchopulmonary dysplasia, congenital heart disease, pulmonary hypertension prior to endotracheal intubation or other diseases that could explain pulmonary hemorrhage, should be ruled out. Patients presenting with sudden pulmonary hemorrhage, with or without respiratory distress and with or without significant findings on chest x-ray, are probable cases (2).

Regarding the cases presented here, patients met the criteria: they were infants between 7.5 and 9 weeks of age, with evidence of airway bleeding, severe respiratory distress requiring endotracheal intubation, mechanical ventilation and bilateral infiltrates on chest x-ray. Given the favorable response to management, fibrobronchoscopy and bronchoalveolar lavage were not needed. No history of lung disease was found and heart disease was discarded.

In the first case, platelets were normal and clotting time was abnormal after the cardiac arrest. No new episodes occurred and, therefore, no further studies were conducted to verify bleeding disorders. In the second case, platelets and clotting times were normal; renal function was normal, there were no findings that indicated physical abuse and no significant gastrointestinal symptoms were found, hence, no digestive tract endoscopy was performed. Finally, no studies were conducted to find autoimmune diseases because of the patients' age and adequate evolution.

Investigation on AIPH patients should include studies for the diagnosis of autoimmune diseases, since some of them may initiate with pulmonary hemorrhage. In the French series with 25 IPH patients, 68% of them early on, and 6 more during follow-up, presented autoimmune antibodies; the most frequent were anti-smooth muscle antibody (50%), antinuclear antibodies (45%) and anti-neutrophil cytoplasmic antibodies (40%). These are related to vasculitis and systemic autoimmune diseases, whose identification and treatment are important for prognosis. It has further been described that one of every four patients surviving IPH is subsequently diagnosed with an autoimmune disease. Differential diagnoses and possible diagnostic aids are presented in Table 1.

Table 1. Differential diagnoses.

DIFFERENTIAL DIAGNOSES		
System or indication	Disorders found	Tests
Pulmonary	▪ Bronchopulmonary dysplasia ▪ Primary ciliary dyskinesia ▪ Bronchiectasis ▪ Cystic fibrosis ▪ Chronic aspiration ▪ Gastroesophageal reflux disease ▪ Diffuse alveolar injury	▪ X-ray or chest CT ▪ Bronchoscopy with bronchoalveolar lavage (BAL) to measure the percentage of hemosiderophages, lipid-laden macrophages and differential cells.
Cardiovascular	▪ Pulmonary hypertension ▪ Congenital heart disease ▪ Myocarditis ▪ Pulmonary vascular congestion ▪ Mitral stenosis ▪ Congestive heart failure ▪ Veno-occlusive disorders ▪ Hemangiomas ▪ Vasculitis	▪ Echocardiogram ▪ Immunological studies
Hematology	▪ Thrombocytopenia ▪ Acquired or congenital coagulopathies ▪ Disseminated intravascular coagulation	▪ Blood count ▪ Clotting times ▪ Reticulocyte count
Gastrointestinal	▪ Celiac Disease	▪ Transglutaminase immunoglobulin A and E
Immunological	▪ Heiner syndrome ▪ Wegener's granulomatosis ▪ Tuberous sclerosis ▪ Lymphangiomatosis or lymphangioleiomyomatosis ▪ Pulmonary-renal syndrome ▪ Systemic lupus erythematosus ▪ Goodpasture syndrome	▪ Test for milk cow protein allergy ▪ Immunoglobulin ▪ Anti-gliadin antibodies (Abs) ▪ Anti-endomysial antibodies (EMA) ▪ Anti-nuclear antibody ▪ Anti-dsDNA antibodies ▪ Anti-smooth muscle antibody ▪ Rheumatoid factor ▪ Anti-neutrophil cytoplasmic antibody ▪ Anti-glomerular basement membrane ▪ Complement ▪ Immune complex
Infectious	▪ Pulmonary or systemic infections	▪ Chest X-ray ▪ Cultures for bacteria, fungi and viruses in BAL ▪ Blood cultures
Physical abuse	▪ Suspected in repeated or unexplained trauma	▪ X-ray of long bones, rib and column grid

Source: Adapted from Taytard *et al.* and from 'Acute idiopathic pulmonary hemorrhage among infants. Recommendations from the working group for investigation and surveillance' (2,5).

Treatment

Management during the acute phase is supportive with mechanical ventilation, packed red blood cell transfusion if anemia is present, hemodynamic support and intravenous steroids. Methylprednisolone at a dose of 1 mg/kg every 6 hours or bolus in the first 3 to 5 days is used depending on the severity and the response. Then, prednisolone 1mg/kg/day is given; continuation or discontinuation is based on evolution. This medication can be used on outpatient daily, or with monthly boluses, according to clinical and laboratory findings. Steroids have shown to decrease the risk of pulmonary fibrosis (7). In life-threatening cases or with severe diffuse alveolar hemorrhage, which does not improve with intravenous steroids, the use of intrapulmonary recombinant factor VIIa has been described with good results in small case series (15).

In chronic cases with poor response to steroids due to steroid resistance or dependency, immunosuppressive agents such as azathioprine, hydroxychloroquine, methotrexate and cyclophosphamide have been used with variable results (7).

The outcome in these diseases may result in death; for example, in the Cleveland series, 5 out of 30 children died and in France, 2 out of 25 died during the acute phase of the disease. In the last series, the average follow-up time was 5.5 years, with good results in pulmonary function in 23 of them.

Patients in our series had a satisfactory clinical evolution: extubation was achieved early. One of them was discharged with oxygen by nasal cannula, and the other with oral steroid. During follow-up, the first case was assessed at 39 months of age and was healthy; the second case is unknown.

CONCLUSIONS

Acute idiopathic pulmonary hemorrhage is a condition that seriously threatens life, therefore, it is important to have a high index of suspicion in infants under one year of age, who were previously healthy, with a sudden onset of airway bleeding related to severe respiratory distress, with high mechanical ventilation requirement and chest x-ray infiltrates. Management with intravenous steroids allows successful bleeding resolution in most cases, so its administration must be timely. For this, the necessary tests must be performed to rule out other causes of diffuse alveolar hemorrhage whose treatment is different. Early diagnosis of this disease, which threatens life, allows adequate therapeutic approach, reducing its morbidity and mortality.

CONFLICT OF INTERESTS

None stated by the authors.

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