Pulmonary Capillaritis in Monozygotic Twin Boys

abstract

Pulmonary hemorrhage can be classified as either proximal or distal (alveolar). Causes of proximal hemorrhage include infection, foreign body aspiration, pulmonary embolus, trauma, vascular malformation, and pulmonary hypertension. Causes of distal or diffuse alveolar hemorrhage are divided by the histologic presence or absence of capillaritis, which is characterized by inflammation of the alveolar interstitium and pulmonary capillary structure. Pulmonary capillaritis is a rare event in children and is associated with higher morbidity and mortality than diffuse alveolar hemorrhage without capillaritis. This is a report of 17-month-old previously healthy monozygotic twins presenting simultaneously with diffuse alveolar hemorrhage, pulmonary capillaritis, and an otherwise negative serologic workup. This suggests a role of genetic predisposition in this rare disease. Pediatrics 2013;132:e1445–e1448

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KEY WORDS
diffuse alveolar hemorrhage, pulmonary hemorrhage, pulmonary capillaritis

ABBREVIATIONS
ANA—antinuclear antibody
ANCA—antineutrophil cytoplasmic antibody
DAH—diffuse alveolar hemorrhage
ESR—erythrocyte sedimentation rate
GBM—glomerular basement membrane
IPH—idiopathic pulmonary hemorrhage
PC—pulmonary capillaritis

Drs Kupfer, Ridall, and Hoffman were responsible for care of the patients and drafted the initial manuscript; Dr Dishop was responsible for the pathologic diagnosis, provided photomicrographs, and contributed to the manuscript; Drs Soep, Wagener, and Fan were responsible for care of the patients, provided mentorship, and contributed to the manuscript; and all authors approved the final manuscript as submitted.

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Diffuse alveolar hemorrhage (DAH) is a rare, often fatal disease in children. In some cases, DAH is accompanied by pulmonary capillaritis (PC), a distinct histologic feature characterized by neutrophilic invasion and fibrinoid necrosis of alveolar capillary walls. The most common cause of DAH without capillaritis is idiopathic pulmonary hemosiderosis (IPH), which is a diagnosis of exclusion and generally carries a better prognosis than DAH with PC. In contrast, PC is more difficult to treat and is associated with higher morbidity and mortality. PC may be isolated or may be a component of systemic vasculitis such as microscopic polyangiitis, granulomatosis with polyangiitis (previously called Wegener granulomatosis), Goodpasture syndrome, systemic lupus erythematosus, Henoch-Schönlein purpura, immunoglobulin A nephropathy, and antiphospholipid antibody syndrome. PC is also associated with certain drugs, including phenytoin, propylthiouracil, and retinoic acid. The clinical presentation of DAH with PC may be acute or insidious and most often includes hypoxemia, radiographic abnormalities (alveolar or mixed alveolar/interstitial patterns), anemia, and elevated erythrocyte sedimentation rate (ESR). In children, PC may be accompanied by lower respiratory tract symptoms, including cough or wheeze, and hemoptysis. Diagnosis of DAH may be suspected based on clinical symptoms, radiographic findings, and the presence of hemosiderin-laden macrophages on bronchoalveolar lavage. These features do not distinguish between DAH with and without capillaritis. Diagnosis of PC may be confirmed by positive serologic studies, such as antineutrophil cytoplasmic antibody (ANCA), antinuclear antibody (ANA), or antiglomerular basement membrane antibody (anti-GBM). However, if these studies are negative, lung biopsy is required for diagnosis.

CASE DESCRIPTIONS

Twin A was a 17-month-old monozygotic twin boy who presented to a local emergency department with several days of fever, nasal congestion, and rhinorrhea. He was mildly hypoxemic, was diagnosed with infectious bronchiolitis, and was admitted to the hospital for supplemental oxygen and supportive care. He had no significant past medical or surgical problems, was not on any medications, and had no exposure to tobacco smoke, fumes, or other irritants. His father had type 1 diabetes and hypothyroidism. On the morning after admission, he was discharged on supplemental oxygen. Given his brother’s condition (see below), evaluation 1 day after discharge showed he was anemic (hemoglobin 6.3 g/dL), with an otherwise normal complete blood count. A chest radiograph showed patchy bilateral opacities (Fig 1A). He was admitted, and evaluation included normal results for urine analysis, coagulation, ESR (11 mm/hour), C-reactive protein (<0.5 mg/dL), ANA, ANCA, anti-GBM, and antiphospholipid antibodies. His nasal polymerase chain reaction was positive for rhinovirus. An echocardiogram was normal and did not show pulmonary venous disease or evidence of pulmonary hypertension. He was given 1 dose of intravenous methylprednisolone, and a lung biopsy was obtained. This biopsy showed patchy alveolar hemorrhage, focal intraalveolar fibrin,
and associated foci of neutrophils infiltrating the alveolo-interstitial compartment, typical of acute pulmonary capillaritis. Focal fibroblastic reaction (organizing pneumonia) also reflected alveolar wall injury, a common associated finding in PC (Fig 2). His treatment is described in Table 1, in addition to which he received red blood cell transfusions. Bleeding ceased after several days of IV corticosteroids. He was discharged 6 days later breathing ambient air. Two months after treatment, a chest radiograph showed near-complete resolution of abnormal interstitial and alveolar markings (Fig 1B). Four months after the initial illness, he remained on therapy and was asymptomatic and normoxic.

Twin B presented at the same time as his brother with similar symptoms of fever, nasal congestion, and rhinorrhea. He was also admitted for bronchiolitis with hypoxemia. He had no previous significant medical or surgical problems, was not on any medications, and there were no unusual exposures. Over the next 24 hours, he developed progressive respiratory distress and hypoxemia. He produced a small amount of blood-tinged sputum and had a hemoglobin of 3.3 g/dL. The remainder of the complete blood count was normal. A chest radiograph showed patchy bilateral opacities (Fig 1C). Polymerase chain reaction of nasal secretions was positive for rhinovirus. Due to anemia and respiratory distress, he was transferred to the PICU and treated with noninvasive ventilation and red blood cell transfusions. Bronchoscopy revealed blood in the central airways. Bronchoalveolar lavage fluid analysis showed 1787 white blood cells (88% neutrophils), 412 050 erythrocytes, a lipid index of 0, and an iron index of 10; all cultures were negative. Because of progressive respiratory failure, he was intubated and required mechanical ventilation for 12 days. He required high positive end-expiratory pressure (up to 14 cm H2O) as well as high oxygen (fraction of inspired oxygen up to 1.0). Urine analysis and blood coagulation studies were normal. C-reactive protein was 4.6 mg/dL, and ESR was 33 mm/hour. ANA, ANCA, anti-GBM, and anti-phospholipid antibodies were negative. Lung biopsy was not obtained because of the patient’s critical illness and clinical instability. He was treated empirically based on his brother’s parallel presentation and lung biopsy findings. He was treated as described in Table 1, and bleeding ceased after initial therapy. Two months after treatment, a chest radiograph showed near-total resolution of abnormal interstitial and alveolar markings (Fig 1D). Four months after the initial illness, he remained on therapy and was asymptomatic and normoxic.

**DISCUSSION**

This unique simultaneous presentation of PC in identical twins raises the possibility of a 2-hit hypothesis: a genetic predisposition for PC combined

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**TABLE 1 Treatment Regimens**

<table>
<thead>
<tr>
<th>Twin A</th>
<th>Twin B</th>
</tr>
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<tbody>
<tr>
<td><strong>Initial</strong></td>
<td><strong>Initial</strong></td>
</tr>
<tr>
<td>Methylprednisolone 30 mg/kg/dose IV for 3 d followed by prednisolone 1 mg/kg/dose every other day PO</td>
<td>Plasmapheresis daily for 3 d</td>
</tr>
<tr>
<td>IVIG 1 g/kg once</td>
<td>Methylprednisolone 30 mg/kg/dose IV for 3 d, followed by prednisolone 2 mg/kg/day PO</td>
</tr>
<tr>
<td>Hydroxychloroquine 4 mg/kg/day PO</td>
<td>IVIG 1 g/kg once</td>
</tr>
<tr>
<td><strong>Outpatient maintenance (4 months)</strong></td>
<td>Cyclophosphamide 2 mg/kg/day PO</td>
</tr>
<tr>
<td>Methylprednisolone 30 mg/kg once a month IV</td>
<td>Methylprednisolone 30 mg/kg once a month</td>
</tr>
<tr>
<td>IVIG 1 g/kg once a month</td>
<td>IVIG 1 g/kg once</td>
</tr>
<tr>
<td>Prednisolone 1 mg/kg/dose every other day PO</td>
<td>Prednisolone 1 mg/kg/day PO</td>
</tr>
<tr>
<td>Hydroxychloroquine 4 mg/kg/day PO</td>
<td>Cyclophosphamide was decreased to 1 mg/kg/dose PO once weekly due to bone marrow suppression</td>
</tr>
<tr>
<td><strong>Weaning</strong></td>
<td><strong>Weaning</strong></td>
</tr>
<tr>
<td>Prednisolone was weaned slowly to 0.4 mg/kg/dose every other day PO</td>
<td>Prednisolone was weaned slowly to 0.4 mg/kg/dose every other day PO</td>
</tr>
<tr>
<td>Hydroxychloroquine was continued at 4 mg/kg/day PO</td>
<td>Cyclophosphamide was replaced with azathioprine 2 mg/kg/day PO</td>
</tr>
</tbody>
</table>

IV, intravenous; IVIG, intravenous immunoglobulin; PO, by mouth.
with an environmental trigger. The father's history of autoimmune disorders also supports the concept of genetic predisposition. Although serologic testing for systemic vasculitides was negative, these tests are limited in identifying an underlying disease. In fact, previous case reports have demonstrated alveolar hemorrhage may be the presenting sign in systemic vasculitic diseases, with seropositivity occurring in the future. New techniques in genetic testing (eg, whole exome sequencing) have identified a genetic basis of previously unexplained diseases but have not been applied to PC.

Several cases of familial IPH have been reported, as have other potentially immune-mediated causes of DAH. These reports are limited in that many patients did not undergo lung biopsy to look for capillaritis and at least some of these cases may have been due to capillaritis.

Children with DAH, with or without capillaritis, can be mistaken for having more common diseases such as infectious bronchiolitis, pneumonia, or aspiration. A key clinical feature in DAH is the combination of anemia and respiratory symptoms with hypoxemia. Hemoptysis is uncommon in children.

Although the role of respiratory viral infections is unknown, our experience suggests that viral illnesses may be associated with or trigger these bleeding episodes. We did not discover any other exposures that could explain simultaneous disease onset. Children with PC may be critically ill and have higher mortality than children with DAH without capillaritis. Because prognosis is affected by the presence or absence of capillaritis, we recommend that lung biopsy be performed in all children with DAH who do not have serologic evidence of vasculitis.

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