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Зміст

Ключові терміни:
Pulmonary Hemosiderosis
This is an 8 month old male referred to Pediatric Pulmonary Clinic with a chief complaint of chronic cough. The cough has been present for 7 weeks. Initially, it was attributed to a viral illness, but the viral cultures and screen for RSV were negative. The cough improved but did not clear with bronchodilators and an aggressive short course of oral corticosteroids which were instituted for suspected asthma. The symptoms had worsened again after the bronchodilator and steroid trial was discontinued. There is a low-grade fever but no evidence of a new upper respiratory infection. The chest radiographs performed by the patient’s primary care physician shows worsening diffuse patchy consolidations with hyperexpansion. Review of systems reveals a slowing of growth from the 4 month routine well child visit to present. There is no family history of any respiratory disease, chronic or serious medical conditions.

Exam: VS T 37.0, P 140, R 50, BP 100/60, pulse oximetry showed oxygen saturations of 86% in room air. His weight is at the 5th percentile. He is thin, slightly pale, tachypneic with slightly labored breathing. HEENT exam is normal. His chest has symmetrical expansion. There are mild subcostal retractions, but no intercostal or supraclavicular retractions are seen. His heart is tachycardic but regular without murmurs. His breath sounds are coarse on inspiration and expiration throughout. The expiratory phase is slightly prolonged. There is good air exchange. His abdomen is soft, non-distended with normal bowel sounds and no hepatosplenomegaly.

Oxygen is started by mask and he is admitted to the hospital. Bronchodilators and antibiotics are initiated and corticosteroids are resumed. His oxygen saturation only improves slightly with supplemental oxygen. The arterial blood gas shows pH 7.35, pCO2 34, pO2 55 on 2 liters/minute of supplemental oxygen. His CBC shows a mild elevation of the white blood count, a normal platelet count, and an anemia with hematocrit of 26, a mean corpuscular volume of 76, and red cell distribution width of 15. His eosinophil count is modestly elevated. Iron studies show depleted iron stores. His chest radiograph still shows interstitial infiltrates.

His improvement over the next three days is gradual, and his chest radiograph still shows an interstitial pattern. Bronchoscopy is performed. The bronchoalveolar lavage demonstrates a large number of hemosiderin-laden macrophages. Cultures and lipid-laden macrophages are negative.

After further review of his history, he had been constipated on formula for the first few months of life, so he was switched to regular cow’s milk and juice at 3 months of age. The serum IgG precipitins to cow’s milk protein are strongly positive. The diagnosis of Pulmonary Hemosiderosis by Heiner’s syndrome is made. All cow’s milk and milk products are withheld. His clinical condition rapidly improves. His subsequent chest radiograph clears with only persisting streaky consolidations. After one week of corticosteroids, they are discontinued. He is continued on iron supplementation and his anemia slowly resolves. Growth also normalizes over the next 3 months.

Any bleeding from or into the lung will lead to hemosiderin deposits in the lung macrophages. Pulmonary Hemosiderosis (PH) is a term that should be reserved for chronic persistent or recurrent bleeding. It is a complex topic, covering a spectrum of different conditions and disease states. The clinical presentation and course is highly variable. Bleeding can be focal or diffuse. It can occur in the airways, alveoli or parenchyma. It can be from pulmonary (lower pressure) or bronchial circulation (higher pressure). It can be mild or life threatening. While there is no universal agreement in classification, it is useful to categorize PH as either primary or secondary. The following table categorizes the etiologies of Pulmonary Hemosiderosis in children from the standpoint of whether the lung insult is primary or secondary:

1. Primary Pulmonary Hemosiderosis (PPH)
The pathophysiology of pulmonary hemorrhage varies by the etiology. Bleeding can come from inherited or acquired weakness, inflammation or congestion of pulmonary blood vessels; immune reactions or antigen-antibody complex deposition in the lung; invasive or chronic infections, or toxic reactions. Regardless of the, any blood cells in the alveoli, airways or parenchyma, are broken down and the hemoglobin is ingested by local macrophages. Once ingested, the hemoglobin is converted to hemosiderin by lysosomal degradation. It may also activate the local macrophages, followed by an inflammatory cascade, including the recruitment of cells and production of cytokines. These events can produce all types of lung disease, pulmonary consolidations, and lymphadenopathy.

Obstructive disease can be seen as the airways narrow with an increase in edema, mucus production and shedding of epithelial cells into the airway. Bronchospasm (the contraction of smooth muscle surrounding the airways) can be seen. Chronic accumulation of fibrin and collagen deposits can lead to pulmonary fibrosis with decreased pulmonary compliance. This can manifest as a restrictive lung disease pattern.

Pulmonary hemosiderosis is an uncommon finding, but the true incidence is unknown. Primary PH is more common in children. The peak incidence of PH (idiopathic) is between 1-7 years of age at diagnosis, but approximately 15% are diagnosed after 16 years of age. Below the age of 10, the incidence is equally divided between the sexes. After age 10, the male to female ratio is 2:1. There are rare instances of familial clusters reported. In adults, PH is more likely to be secondary in nature.

The classic triad of findings includes pulmonary infiltrates, iron deficiency anemia and hemoptysis (although hemoptysis is seen less commonly in children). Approximately 50% of young children present without pulmonary complaints. When present, complaints include fever, pallor, dyspnea, cough, exercise intolerance and growth failure. Common findings are, tachypnea, tachycardia, cyanosis, clubbing, fine or coarse crackles, wheezing, and hypoxemia. In children with a significant hemorrhage, it may be difficult to determine whether the blood is coming from the upper airway, lower pulmonary system or GI tract. Many patients will have melena from swallowed pulmonary blood.

The radiographic appearance may vary depending on the degree of involvement and chronicity. Plain film chest radiographs may range from normal to demonstrating focal lymphadenopathy or consolidations, or extensive bilateral interstitial disease. Pulmonary function testing may demonstrate an obstructive, restrictive or mixed pattern.

It is common for patients with PH to have a delay in diagnosis. Infectious pneumonia, bronchitis, aspiration, asthma and cystic fibrosis are more commonly seen with many of the same complaints and findings. Having a high clinical suspicion is necessary to make the diagnosis. While a bronchoalveolar lavage finding of a large number of hemosiderin-laden macrophages is diagnostic, it is not the end of the evaluation. Subsequent studies are needed for evaluation of the etiology. IPH is a diagnosis of exclusion, and is only appropriate after a thorough investigation is completed.

Complete blood counts, iron studies and a measure of renal function will be helpful to evaluate the patient's current status. ANA, rheumatoid factor, erythrocyte sedimentation rate, complement levels, immunoglobulins, anti-basement membrane antibodies, and serum precipitins to cow's milk protein should also be included in the evaluation for etiology. A cardiac evaluation including physical exam, EKG and CXR evaluation should be included. A referral to cardiology, rheumatology or hematology should be considered. Some experts advocate a lung biopsy for all patients, to include immunofluorescence and electron microscopy studies. Others reserve this for selected cases.

Each patient should have supportive measures as appropriate to their presentation, including supplemental oxygen, blood transfusion, and antibiotics for cases of secondary infection or suspected infection. Respiratory support includes chest physiotherapy to aid in clearing excess secretions, bronchodilators, CPAP or mechanical ventilation. Patients with ongoing bleeding may benefit from positive end expiratory pressure (PEEP).

Treatment has to be viewed in light of the etiology. For those with PH from exposure and toxins from Stachybotrys, the main treatment is elimination of the offending agent. Diet restriction, especially for
those found to have serum precipitins to milk products, is essential. For those with secondary PH, treating the primary etiology is critical.

Medical therapy is typically aimed at controlling the inflammatory response. Corticosteroids are the mainstay, but there is no study comparing the dosing strategy. The dose is usually started at 2-5 mg/kg/day of prednisone or equivalent. This dose is used for several weeks, or until the hemorrhage is well controlled. The dose is then tapered, and there are many different protocols. Other immunosuppressive agents have been used in an attempt to reduce the prolonged corticosteroid effects, including azathioprine, chloroquine and cyclophosphamide.

If patients are having significant ongoing hemorrhage, a nuclear medicine study with labeled RBCs can be done to help locate the site. For life-threatening bleeds or those patients that don't respond to medical therapy, bronchial artery embolization may be required. For extreme cases removal of an affected segment or lobe may be necessary.

Close monitoring should include growth, oxygen saturation monitoring, hemoglobin and iron studies, chest radiographs, pulmonary function testing (if old enough), and renal function studies throughout recovery. Reinstitution of aggressive corticosteroid or immunosuppressive therapy is typical for breakthrough exacerbations.

The prognosis is variable, related to the cause. For secondary PH, it must include the natural history of the primary disease. A delay in diagnosis will yield a worse prognosis. Early studies showed a very poor prognosis for IPH. The average was approximately 2 years from diagnosis to death. More recent reports suggest an improvement in this statistic with more aggressive management. Additionally, newer technology has provided the means for more extensive evaluation, facilitating specific diagnostic determination (i.e., fewer diagnosis of IPH). Many patients can have sustained or complete remission with newer therapies. Although scarring and fibrosis may be permanent, full compensation is possible, especially in younger patients.

Questions

1. Which of the following findings are not usually present in a patient presenting with pulmonary hemosiderosis?
   a. Fever
   b. Parenchymal consolidations
   c. Hypercarbia
   d. Hypoxemia
   e. Cough

2. Why is it important to classify hemosiderosis as primary or secondary?

3. What kind of lung disease can be seen in pulmonary hemosiderosis?
   a. Obstructive disease
   b. Restrictive disease
   c. Mixed obstructive and restrictive
   d. Any of the above

4. Which of the following is not part of the classic triad of symptoms seen in pulmonary hemosiderosis?
   a. Pulmonary hemorrhage
   b. Anemia
   c. Hemoptysis
   d. Pulmonary infiltrates
   e. None of the above

5. True/False: Lung biopsy is the diagnostic test of choice for idiopathic pulmonary hemosiderosis.

Related x-rays
Available online at: www.hawaii.edu/medicine/pediatrics/pemxray/v3c07.html

Answers to questions

1. c. Hypercarbia is not usually seen because compensatory mechanisms usually overcome the problems of reduced gas exchange by increasing minute ventilation (either by increasing rate or depth of ventilation).

2. It is one scheme to help identify the etiology for a condition with numerous causes. Treatment is more likely to be successful after identifying and treating the primary cause.

3. d. Bronchospasm, edema, and mucus can narrow the airway causing obstructive disease similar
to asthma. Chronic inflammation can increase interstitial fibrin and collagen deposits which then reduce compliance resulting in giving restrictive disease. Any combination of the two is possible.

4. a. The classic triad is iron deficiency anemia, pulmonary infiltrates and hemoptysis, although hemoptysis is seen less commonly in children. "Pulmonary hemorrhage" does result in hemosiderosis, but it is not part of the classic triad.

5. False. There is controversy over whether a lung biopsy should be undertaken for all patients with significant PH. It could be argued that all patients who have PH without a known etiology (suspected IPH) should have a lung biopsy. But since IPH is a diagnosis of exclusion, a lung biopsy doesn't preclude the other parts of the evaluation, including history, exam, radiology and laboratory studies. Pathology from lung biopsy is seldom diagnostic alone and can only be interpreted in light of the other information.