Pulmonary Problems in Pediatric HIV infection

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Pulmonary disease continued to be the most common AIDS-associated complication and the cause of morbidity and mortality among children with HIV infection in developing countries. Pneumonia, diarrhea and malnutrition were the most common causes of death both in children born to HIV-1 infected mothers and in HIV-1 infected children. Pulmonary problem has been the first manifestation of HIV-1 infection in more than half of the cases. Pulmonary manifestations of HIV infection broadly divided into infectious, noninfectious, and malignant categories. The common infectious complication were Pneumocystis carinii pneumonia (PCP), bacterial pneumonia and tuberculosis. Noninfectious complications were lymphoid interstitial pneumonia, bronchiectasis, and diffuse alveolar damage. Neoplastic pulmonary diseases common in the adult AIDS population are rare in the pediatric patient.

Pneumocystis carinii pneumonia

PCP is described as the most common opportunistic infection in children with AIDS in the US. However, data from developing country were scared. PCP can be the initial presentation of HIV infection. The median age of presentation is 5 month. Compared to HIV-infected adults, children with AIDS and PCP are much sicker. Clinical manifestation include acute onset of cough, fever, tachypnea and chest wall retraction. The patient is hypoxemic with low level of oxygen saturation and a normal or low carbon dioxide in the early phase. Most of the patient deteriorated rapidly into respiratory failure. The marked hypoxemia and lack of auscultatory findings in PCP are helpful in suggesting the diagnosis. An elevated LDH level supports the diagnosis. The chest radiograph typical shows a diffuse reticulonodular infiltrate most prominent in the perihilar region and extending peripherally. Air bronchograms, focal infiltrates, and pneumatoceles can also occur. Diagnosis can be made in as many as two thirds of cases by demonstration of cysts or organisms in respiratory secretions. In those who deteriorate rapidly and need ventilatory support from the outset, a bronchoalveolar lavage is performed immediately, along with the start of empiric therapy.

The most effective specific therapy is trimethoprim/sulfamethoxazole (TMP/SMX) at 20 mg/kg/day of TMP intravenously. It may take 4 to 8 days to demonstrate clinical improvement in adult with PCP. Corticosteroids are helpful adjuncts to specific therapy in children and adult. PCP prophylaxis has had a dramatic effect on reducing the incidence of the disease. Primary prophylaxis is suggested if the CD4+ count is low. Drug used for prophylaxis include TMP/SMX at 150 mg/m²/day 3 times a week. If TMP/SMX is not tolerated or cannot be used, alternatives include parenteral or aerosolized pentamidine.

Lymphoid interstitial pneumonia(LIP) and Pulmonary lymphoid hyperplasia (PLH)

Lymphoid interstitial pneumonia (LIP) is regarded as both a disease and a nonneoplastic, inflammatory pulmonary reaction to various external stimuli or systemic diseases. Approximately 30% to 40% of perinatally infected children and 12% of transfusion-related HIV-infected children will have LIP. This condition is not usually seen in HIV-infected children until the second year of their life. The presence of this entity in an HIV-infected child satisfies the CDC surveillance definition for AIDS. HIV can induce proliferation of BALT in vitro. HIV antigen and antibody have been found in BAL and lung tissue specimens of some HIV positive patients with LIP. It appears that a transient lymphocytic alveolitis may develop in every HIV-positive patient group.
Pathologically, LIP/PLH represents a spectrum of disease characterized by a diffuse infiltration of lymphocytes in the interstitium and scattered nodules of mononuclear cells.

Involvement of alveolar and interlobular septal, as well as subpleural and peribronchial lymph channels have been reported. In LIP the infiltration is diffuse throughout the parenchyma. In PLH the infiltration is primarily adjacent to bronchial and bronchiolar walls and consists of bronchial associated lymphoid tissue hyperplasia. The etiology of LIP remains unknown. The pathogenesis of LIP/LPH may represent an atypical response to an inhaled or circulating antigen by a dysregulated immune system as a consequence of HIV infection. An association with Epstein-Barr Virus (EBV) is well described in the literature but the significance of this relationship has not been determined. Simultaneous infection with EBV and HIV may amplify the risk of development of LIP. B lymphocytes infected with EBV are very susceptible to HIV infection in vitro and could enhance intrapulmonary replication of HIV. This would result in further interstitial lymphocyte proliferation.

Clinically, the onset of LIP/LPH is insidious and slowly progressive, it may be associated with cough, lymphadenopathy, hepatomegaly, clubbing of fingers, hypergammaglobulinemia and parotid gland enlargement. Auscultation of the chest may be normal or reveal crackles and wheezes. Chest radiographic findings consist of diffuse reticulonodular or nodular pattern with or without hilar or mediastinal adenopathy.

Serum IgG levels greater than 2500 mg/dL are strongly associated with LIP/PLH. Radiograph typical reveals a diffuse interstitial nodular pattern with or without hilar adenopathy. A presumptive diagnosis of LIP can usually be made clinically and by persistent chest X-ray finding lasting more than 2 month, not responding to antibiotics and without other documented etiologies. Presumptive diagnosis of LIP/PLH can be made based on clinical findings and typical radiographic pattern lasting more than 2 months without another cause. Lung biopsy definitely establishes the diagnosis of LIP/PLH.

Treatment of LIP/PLH is nonspecific. Oxygen is required for hypoxemia episodes. Treatment with corticosteroids has been reported to improve hypoxemia in a small number of patients. The results have been variable. Some patients improve without therapy while others progress to advanced interstitial fibrosis despite immunosuppression. Because LIP supposedly represents an immune response to infection, the natural progression of the disease might alter with the advent of HAART. Recently, improvement in clinical symptoms, radiology and pulmonary function tests have been described in an HIV infected adult patient with LIP treated with combination antiretroviral therapy.

Bacterial infection

HIV-infected children are at risk for severe or repeated bacterial infection. Recurrent or severe pneumonia is often the initial clinical presentation. Predominant organisms associated with pneumonia are *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The symptoms, such as fever, cough and respiratory distress often suggest pneumonia and are associated with hypoxemia.

A positive blood culture may establish the cause of pneumonia in a patient with a new infiltrate on the chest radiograph, There are limitations of diagnosing bacterial pneumonia in children. Initial treatment is empiric, but therapy should be determined by etiologic organisms and antibiotic sensitivity.

There have few reports of *Nocardia asteroides* lung infection in HIV-infected children, although it is a relatively uncommon opportunistic pulmonary infection complicating in HIV-infected patients. The clinical features of pulmonary nocardiosis in HIV-infected patients are similar to those described in other immunocompromized patients. Patients present typically with an indolent course and nonspecific constitutional complaints. Pulmonary symptoms consist of a productive cough, dyspnea, pleuritis chest pain and hemoptysis. Roentgenographic manifestations of nocardiosis are markedly variable, ranging from localized consolidation with or without cavitation, large irregular nodules, solitary masses to reticulonodular infiltrates. Because none of the clinical, laboratory or radiographic
features are pathognomonic, the diagnosis of nocardiosis is often delayed. Since early diagnosis may lead to an improved outcome, it is essential for physicians caring for HIV-infected patients to maintain a high level of suspicion for this pathogen. Definitive diagnosis usually relies on isolation of Nocardi a species from a clinical specimen such as BAL fluid or other body fluid.

**Fungal infection**

Fungal infection, especially mucosal and cutaneous fungal infection, are commonly diagnosed in most HIV-infected children. This condition frequently caused persistent symptoms which can be difficult to eradicate. However, systemic fungal infection are relatively rare in children with HIV diseases. *Candida albican, cryptoccus neoformans, Histoplasma capsulatum, Aspergillus spp.*, coccidioidomycosis, are the common cause of pneumonia.

Intrapulmonary candidiasis can be difficult to diagnose. Unless the patient is intubated, there may be contamination of specimens by upper airway organisms. BAL is usually necessary to confirm the diagnosis. Invasive pulmonary aspergillosis has been reported to occur in HIV-infected children. All of these children died and diagnosis was made after death.

**Viral infection**

Viral pneumonia with common pathogen, such as respiratory syncytial virus (RSV), parainfluenza, Herpes simplex and adenovirus has occurred in HIV-infected children. Infection with RSV, Measles or Varicella causes significant morbidity in normal children but may be life-threatening in the HIV-infected patients.

Cytomegalovirus (CMV) infection is an unusual complication of AIDS in children that can cause retinitis, encephalitis and colitis. It is most commonly found with other pathogens, for instance, concomitant with PCP infection has been found. The presence of CMV infection does not appear to adversely affect outcome and survival in HIV-infected children.

**Tuberculosis**

Children with HIV- infection are more likely to be in contact with HIV-infected adults with tuberculosis and therefore are increasingly susceptible to tuberculosis infection and disease. Pulmonary tuberculosis is the predominant clinical presentation. The presentation and radiographic pattern of tuberculosis in pediatric AIDS patents are commonly atypical. Fever, cough, lobar pneumonia and lymphadenopathy may indicate tuberculous infection. Screening of HIV-infected children with tuberculosis with tuberculin skin testing is recommended. A definite diagnosis can be made from isolation of organism from bronchial lavage fluid, lung tissue, lymph nodes, bone marrows, gastric aspirates, cerebrospinal fluid, or blood,

**Bronchiectasis**

Bronchiectasis is now being seen more frequently in children with HIV infection. Mechanism of development of bronchiectasis include acute or chronic infection a direct effect of HIV on the lung, and persistent atelectasis. Bronchiectasis should be expected when radiographs show persistent abnormalities in the same lobe for more than 6 months. The diagnosis can be confirmed with a computed tomography scan showing dilated tubular structures.

**Diffuse alveolar damage**

Diffuse alveolar damage is a sequence of events following severe acute lung injury. It has been reported in patients with HIV infection. Possible etiologies include viral or opportunistic infections such as P. carinii infection, adult respiratory distress syndrome, and oxygen toxicity. Clinical presentation include progressive respiratory distress and diffuse pulmonary infiltrate. The condition should be suspected if there is persistent hypoxemia following acute respiratory failure from PCP or other
opportunistic infection.

**Pulmonary tumors**

Kaposi's sarcoma, pulmonary tumor of smooth muscle origin such as Leiomyoma, Leiomyosarcoma, and lymphoma have been reported in pediatric age group. Most cases of Kaposi's sarcoma usually occur in adolescent. The clinical presentation varies from indolent skin disease to disseminated visceral involvement. Pulmonary involvement cause dyspnea, cough and fever. The chest radiograph can show an interstitial pattern, which is usually homogenous or nodular infiltrate. Pleural effusions are common. The diagnosis is made by biopsy.

**Upper airway disease**

Upper airway obstruction in children with HIV infection has been reported that usually resulted from lymphoid proliferation such as tonsillar and adenoidal hypertrophy and pharyngeal infiltration.
Appendix: Approach to an HIV-infected child with persistent pulmonary infiltrastion

**Asymptomatic HIV-Infected child with persistent reticulonodular pattern on chest X-ray**

- Monitor clinical status and oxygen saturation every month
- Repeat chest X-ray every 3-6 months

**Acute respiratory symptoms & signs and/or evidence of acute pyogenic infection (e.g. elevated WBC, rales)**

- Obtain respiratory secretions for histopathology and culture, including AFB
- Obtain blood cultures
- Place PPD
- Obtain blood gases or pulse oximetry
- Initiate empiric therapy for PCP and bacterial pneumonia

**Chronic, progressive respiratory symptoms and signs**

- Obtain respiratory secretions for histopathology and culture including AFB
- Consider aspirates x3 for AFB
- Place PPD

**Non-diagnostic**

- Cultures or histologic examination positive for specific pathogen (e.g. PCP, bacterial pathogen, etc.)
- Initiate specific therapy for pathogens identified
- Bronchoscopy or open lung biopsy to obtain tissue for pathologic examination
- If TB diagnosis confirmed or highly suspected, initiate treatment for TB
- Initiate Rx for other specific pathogens