Follicular Bronchitis in the Pediatric Population*

Bernard T. Kinane, M.D.; Anthony L. Mansell, M.D.; Robert G. Zuerdling, M.D.; Allen Lapey, M.D.; and Daniel C. Shannon, M.D.

Five patients in a pediatric population were identified with idiopathic follicular bronchitis (IFB) by open lung biopsy and their case records were reviewed. All were tachypneic and had a chronic cough by 6 weeks of age. The physical examination was characterized by diffuse fine crackles in four patients and by coarse rhonchi in one. The chest radiographs in all demonstrated a diffuse interstitial pattern. None had a collagen vascular or an autoimmune disease demonstrable. Response to corticosteroid therapy was minimal. Associated or coincidental esophageal reflux was treated surgically in two. No viral or bacterial agents were isolated in the sputum or the biopsy specimens.

Lymphoid hyperplasia is a common phenomenon at many sites in the body. It is frequently found in the lungs after airway infection. There exists a group of patients with pulmonary lymphoid hyperplasia, idiopathic follicular bronchitis (IFB), in whom no cause is immediately obvious. This entity is rare in the adult literature and to our knowledge only one case has been reported in a child. Lymphoid hyperplasia is observed along the bronchioles, with reactive germinal centers at the bifurcation in a normal anatomic pattern for bronchial-associated lymphoid tissue. In the adults with this condition, one third have a connective tissue disease, one sixth have an autoimmune disease, and the remaining have no known association. An infectious etiology is possible but has not been established.

Methods

Patients were identified by the physicians of New England Pediatric Pulmonary Consortium and all patients’ records were reviewed. Diagnosis was confirmed by open lung biopsy specimen. AIDS and cystic fibrosis were excluded.

Case Reports

Case 1

A white female patient had onset of episodic respiratory distress (an event in which there is tachypnea associated with subcostal retractions) at 6 weeks of age. This was associated with a persistent cough and pyrexia. Each episode lasted about 3 weeks and she was treated on an outpatient basis with bronchodilators and antibiotics. She had six such episodes over the first year. Between episodes, tachypnea persisted. She grew at a normal velocity. Examination was characterized by fine crackles in both lung bases that were more diffuse during exacerbations but were present also when the child was asymptomatic. Chest radiograph showed an interstitial pattern of infiltration with normal lung volumes. Results of barium swallow, echocardiogram, and pH probe were normal. Laboratory evaluation included a normal sweat chloride test, no growth or identification of bacteria or viruses from any body fluids, normal white blood cell count and differential, and normal immunoglobulins. Human immunodeficiency virus (HIV) antibodies in serum were negative. Open-lung biopsy specimen at 1 year of age revealed follicular lymphocytic infiltrate surrounding and focally infiltrating the bronchial walls. The infiltrate did not extend into the interstitium and no intra-alveolar exudate was present.

There was no response to treatment with antibiotics, bronchodilators, or steroids (two courses of 1 mg/kg/d for 10 days). The patient is now 2 years of age and by 18 months her exacerbations became less frequent and decreased in severity. Growth continues at a normal velocity.

Case 2

A 3.8-kg full-term white female infant who was delivered vaginally developed transient tachypnea of the newborn requiring oxygen for 18 h. She had nine episodes of respiratory distress during the first year and 14 over the next year but none required hospital admission. Each episode was characterized by fever and fine crackles in both bases; the crackles have persisted. Family history was positive for a brother with mild asthma and a paternal aunt with common variable immune deficiency that was treated with γ-globulin. Chest radiograph revealed decreased lung volumes and a fine interstitial pattern. Laboratory evaluation included a normal sweat chloride test, normal total blood cell count, and no growth or identification of bacteria or viruses from blood sputum or open-lung biopsy material (including cytomegalovirus and Mycoplasma). Results of an immune evaluation were normal (including negative HIV antibodies) except for a slightly low IgG (32 mg/dl at 2.5 years). Barium swallow and pH probe were normal.

Open lung biopsy was performed at 3 years of age. The histologic findings were almost identical to the previous case. She was treated with four courses of steroids and bronchodilators with minimal response. She was treated with intravenous γ-globulin between years 5 and 7 for 9 months of the year which seemed to ameliorate

AIDS = acquired immunodeficiency syndrome; FEV1 = forced expiratory volume in 1 s; FVC = forced vital capacity; HIV = human immunodeficiency virus; IFB = idiopathic follicular bronchitis; PFTs = pulmonary function tests; RV = residual volume; TLC = total lung capacity
symptoms. Also, prophylactic antibiotic therapy was initiated during the eighth year with minimal improvement. She developed clubbing at 4 years of age and her examination has always been characterized by crackles. She began to improve in her third year and now at 8 years of age has had a decreased number of acute exacerbations; she has had no recent hospital admissions. Despite her improvement in symptoms, her growth has been poor; weight and height have been consistently below the fifth percentile. Pulmonary function tests (PFTs) at 8 years of age revealed a vital capacity of 76 percent of predicted. The ratio of FEV1/FVC was 53 percent and flows at 50 and 75 percent of exhaled vital capacity were 22 and 18 percent of predicted, respectively. The residual volume (RV) was not measured. There was no improvement in air flow rates following the administration of bronchodilator by aerosol.

Case 3

This female infant was noted to have hydrops fetalis of unknown etiology at birth and was delivered at 36 weeks gestation with a birth weight of 2.9 kg. Pregnancy was normal except for polyhydramnios. The baby developed mild respiratory distress at birth that was treated with hood oxygen for 2 days. She was believed to have pneumomitis but all cultures were negative. Respiratory rate returned to normal but a loose cough persisted. The infiltrates found on chest radiograph persisted and she was discharged from hospital at 4 weeks of age. During the first year, she had frequent acute episodes of wheezing associated with fever that were treated with antibiotics and bronchodilators. Examination was characterized by coarse rhonchi. These episodes were associated with weather changes and exposure to cigarette smoke. Results of laboratory evaluation at 6 months included normal sweat test and serum immunoglobulins.

During the first 4 years, she had eight exacerbations per year but had only one admission to hospital. At about 4 years of age, her symptoms began to improve. She continued to have a daily cough particularly in the morning. Her chest radiograph showed marked hyperinflation with peribronchial thickening. The PFTs revealed a vital capacity of 67 percent of predicted. The ratio of FEV1/FVC was 76 percent and flows at 50 and 75 percent of exhaled vital capacity were 30 and 18 percent of predicted, respectively. The ratio of RV to total lung capacity (TLC) was 67 percent. Following the administration of aerosolized bronchodilators, there was no improvement in airflow. Nevertheless, she was then placed on a regimen of intensive bronchodilator therapy and a course of prednisone at 1 mg/kg/d for 10 days. Following this, there was a moderate improvement in her symptoms. Repeated PFTs demonstrated improved flow rates but the RV was unchanged. She was maintained on a regimen of regular bronchodilators with inhalated corticosteroids. While receiving this regimen for 6 months, her symptoms increased and results of PFTs deteriorated. She was reinvestigated. PH probe revealed prolonged gastroesophageal reflux after meals. Bronchoalveolar lavage was normal with 82 percent of the cells being macrophages. Microscopy of an open lung biopsy specimen showed severe peribronchial lymphoid infiltrate with an intraluminal purulent exudate and rare mucus plugs. No lipid components were noted. Patchy atelectasis and emphysema were also noted.

She was initially treated with metoclopramide and ranitidine with no change. She had a fundoplication and following this there was a slight improvement in her symptoms. She is now 11 years old and her condition has continued to improve with only two acute exacerbations per year.

Case 4

A male infant was delivered at full term with a birth weight of 4.1 kg. Pregnancy was complicated by maternal surgery for an abdominal abscess during the first trimester. Mother was treated with erythromycin and sulfisoxazole (Gantrisin); she developed an allergic response to the latter. He was noted to have increased respiratory rate at about day 10. Respiratory distress became more significant and at 6 weeks he had his first admission to hospital. There were nine similar admissions in the first year and on each occasion he was febrile. His examination was characterized by wheeze and diffuse fine crackles. Chest radiograph revealed diffuse perihilar densities with interstitial pattern throughout the lung parenchyma. On two occasions, he required nasal oxygen, and between 9 and 12 months, he required oxygen at home. He had a good response to bronchodilators and corticosteroids. Laboratory evaluation included a normal sweat chloride test, normal total blood cell count, and no growth or identification of bacteria or viruses from blood, sputum or open-lung biopsy material. Results of an immune workup were normal (including HIV antibodies titer). Barium swallow was normal. Biopsy specimen at 3 years of age was characteristic of IFB and there was no evidence of pneumonia. Mother and a maternal aunt had moderate asthma. He is now 15 years of age and has been reviewed at 6-month intervals since infancy. His symptoms have gradually improved over the years with the most marked improvements occurring between three and four years of age. His weight and height increased from the 25th percentile at 3 years to the 75th percentile at 7 years. Before 3 years of age, he had five admissions per year but this has now decreased to two. He had crackles on examination at all times until 14 years of age. His baseline PFTs reveal an FEV1 of 80 percent and FVC of 105 percent of predicted. The FEV1/FVC was 72 percent which improves to 90 percent with bronchodilators. He experiences mild exercise intolerance.

Case 5

This patient was the product of a normal pregnancy and was delivered vaginally at term with a weight of 4.9 kg. At 6 weeks of age, he was noted to be tachypneic with a rate of 88/min but his weight gain was appropriate. Results of his examination at this time were otherwise normal so no treatment was initiated. At 4 months, his symptoms were significantly worse. He had a persistent cough, mild respiratory distress, was not gaining weight, and had projectile vomiting. Examination was characterized by crackles in all lung fields. His chest radiograph suggested a bilateral interstitial process with normal lung volumes. Barium swallow revealed significant reflux and he had a gastrostomy and fundoplication performed. Two months after the procedure, there was no improvement in his respiratory symptoms. Sweat chloride and immunoglobulins were normal; PPD was negative with a positive control and an extensive immune workup including HIV titer was negative. Some mild improvement occurred over the next 6 months, but findings from his examination remained unchanged. An open-lung biopsy specimen showed the same characteristics as case 3. His symptoms continued and at 2 years he was placed on a regimen of prednisone, 2 mg/kg, on alternate days for 6 months. There was minimal improvement on this regimen. However, between 3 and 4 years, there was a significant improvement in his symptoms. At 9 years, the child is thriving and has only occasional episodes of cough. Crackles continue to be heard over both lung bases on deep inspiration.

The PFTs revealed a mild obstructive defect with a vital capacity of 58 percent of predicted, FEV1/FVC of 60 percent, and flows at 50 and 75 percent of exhaled vital capacity were 60 and 53 percent of predicted, respectively, with a mild improvement after inhaled bronchodilator. The ratio of RV to TLC was increased to 60 percent.

Results

Five patients were identified of which three were male (Table 1). All patients were symptomatic by 6 weeks of age and had peak symptoms between 6 and 18 months. Cough associated with moderate respiratory distress was seen in all patients. Four patients
had frequent recurring pyrexia of unknown origin. Four patients had diffuse fine crackles on examination and the other had coarse ronchi. All patients had an interstitial pattern on chest radiograph; lung volumes were variable. The histologic findings were characteristic with follicular lymphoid hyperplasia around the bronchus (Fig 1) and between the bronchiole and the pulmonary artery in all patients. These follicles have germinal centers and frequently compress the bronchial lumen. A concentric ring of lymphocytes surrounded the bronchioles. The bronchiolar lumen had minimal acute supplicative exudates and rare mucous plugs in two cases.

In an effort to establish a cause, each patient had extensive testing to rule out immune deficiency, collagen vascular disease, and viral causes. Only in one patient was an abnormality demonstrated (slightly decreased IgG). Two patients were found to have esophageal reflux that was treated surgically. Viral and bacterial cultures of sputum and lung tissue were negative. Titers were negative for Mycoplasma and for a number of viruses, including adenovirus and Epstein-Barr viruses. The use of polymerase chain reaction to establish a viral cause was not possible because of the method used to fix biopsy material.

Patients were followed up for 2 to 15 years (>7 years in 4). Four patients had a minimal response to bronchodilators and to steroids. The conditions of all improved between 2 to 3 years of age. In the case of the two patients who had a surgical procedure for esophageal reflux, the improvement did not occur for at least 6 months after the procedure. All patients older than 7 years have chronic mild obstructive airways disease (mean FEV1/FVC 71 percent).

**DISCUSSION**

Idiopathic follicular bronchitis is similar to viral-induced bronchiolitis in clinical presentation, but differs in that crackles persist and recurrence of symptoms is common. The clinical course also resembles cellular interstitial pneumonitis which presents at birth and improves gradually over the first 4 years. This may reflect a similar cause or simply improvement with growth and development. All but one patient with IFB had diffuse fine crackles that persisted, a finding that is very unusual in the first year and should suggest this diagnosis. All patients are left with mild airways disease that may arise from airway injury over a protracted period. This group of patients has a more favorable prognosis than the four children described by Yousem et al. However, their cases were found in the setting of immune deficiency or autoimmune disease and two developed progressive lung disease.

Follicular bronchiectasis was used by Whitwell to describe extensive formation of lymphoid follicles in the walls of bronchi with bronchiectasis. This occurred most commonly in children and he postulated that this was a sequel of acute infections such as measles, whooping cough, or influenza. Such cases were also found in association with adenovirus. Yousem et al
described similar histologic changes without bronchiectasis. This occurred in patients with autoimmune disease or immunodeficiency states, including AIDS. However, in nearly half of the patients, no microbial or clinical association was found. Our patients fall into this latter group with the possible exception of case 2.

The cause was not established, but an infectious agent is probable in view of the histologic pattern. Because of the early presentation, an intrauterine origin is suggested. Hydrops fetalis in case 3 would be consistent with this. A similar histologic picture is seen in animals with infections induced by *Mycoplasma pneumoniae* and a number of viral agents. However, the serologic study and cultures were not helpful in our patients. To establish an etiology, all future patients shall be investigated using molecular techniques. Idiopathic follicular bronchitis may also represent a response to nonspecific injury such as reoccurring aspiration. The finding of a similar histologic pattern in autoimmune diseases, tumor, cystic fibrosis, and bronchiectasis would buttress this theory. Two of our patients who were treated surgically for esophageal reflux showed slow improvement. However, this reflux may also reflect the larger than normal transmural esophageal pressure with each breath. Also, in case 3, there were no lipid-laden macrophages that make aspiration an unlikely cause. It was our impression that the esophageal reflux was secondary and the improvement in lung symptoms following surgery was coincidental with the normal spontaneous improvement.

We have identified a characteristic form of bronchiolitis beginning at 6 weeks, characterized by persistent crackles and mild residual lung disease whose cause is unknown.

**REFERENCES**