CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 37-2011: A 9-Month-Old Boy with Recurrent Tachypnea and Respiratory Distress

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PRESENTATION OF CASE

Dr. Sze Man Tse (Pediatrics): A male infant was admitted to this hospital at the age of 5.5 months, because of tachypnea and respiratory distress.

The patient had been well until 2 days earlier, when cough and somnolence developed. The night before admission, the temperature rose to 38.6°C; acetaminophen was administered. The next morning, labored breathing was observed, and his family noted blotchy areas on his face and that his "chest was sucking in" more than usual. Oral intake decreased, nonbloody diarrhea (four or five episodes) developed, and urination decreased. On examination by his pediatrician that afternoon, the respiratory rate was 30 to 50 breaths per minute, with chest retractions, and the oxygen saturation was 85 to 87% while the patient was breathing ambient air. Albuterol was administered by nebulizer, and he was transported to the emergency department at this hospital.

The patient was born after a full-term gestation by scheduled repeat cesarean section, and he had been well except for one febrile episode at the age of 89 days. He had received all routine childhood immunizations through 4 months of age, took no medications, and had no known allergies. He lived with his mother, one sibling, and maternal relatives and attended day care. There were no pets in the house. His father, maternal grandmother, paternal grandfather, and sibling had asthma; his mother smoked cigarettes outside the home.

On examination, the weight was 7.2 kg (10th percentile), the temperature 36.4°C, the blood pressure 106/57 mm Hg, the pulse 160 beats per minute, the respiratory rate a maximum of 52 breaths per minute, and the oxygen saturation 90% while the patient was breathing ambient air. Nasal flaring and supraclavicular and subcostal retractions with respirations were present; there were coarse expiratory wheezes bilaterally and decreased breath sounds on the right side. The remainder of the examination was normal. A complete blood count, measurements of serum electrolytes and calcium, tests of renal function, and a urinalysis were normal. Testing for influenza, parainfluenza, adenovirus, and respiratory syncytial viruses was negative. A chest radiograph showed mildly increased lung volumes, bilateral perihilar interstitial opacities, and peribronchial cuffing. Oxygen was administered by a nonre-

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breather face mask; the oxygen saturation rose to 96 to 98%. Methylprednisolone, 2 mg per kilogram of body weight, was administered intravenously, and albuterol was given by nebulizer. The patient was admitted to the pediatric service, and intravenous crystalloid was administered; prednisolone (2 mg per kilogram per day) was given orally, and ceftriaxone (360 mg) was administered intravenously. A blood culture was sterile. His condition improved, and he was discharged on the third day, taking albuterol and budesonide by nebulizer and prednisolone (a 5-day course) orally.

During the next week, cough persisted, nasal congestion increased, and oral intake and urination gradually decreased. Eleven days after discharge, the patient returned to the emergency department. On examination, the pulse was 150 beats per minute, the respiratory rate 24 breaths per minute, and the oxygen saturation 90% while he was breathing ambient air; the temperature was normal. Mild rhinorrhea was present, and coarse breath sounds were heard bilaterally, without wheezing or prolongation of the expiratory phase. The remainder of the examination was normal. A complete blood count was normal, as were tests of renal and liver function and measurements of serum electrolytes, glucose, phosphorus, magnesium, total protein, albumin, and direct and total bilirubin. Chest radiographs revealed hyperinflated lungs, with peribronchial thickening.

The patient was readmitted to the hospital; supplemental oxygen, prednisolone, intravenous fluids, and saline nebulizer treatments were added. Testing for respiratory viruses was negative. Intermittent tachypnea and a supplemental oxygen requirement persisted. On the sixth day, auscultation of the lungs revealed coarse breath sounds and fine crackles. Glucocorticoid administration was increased (prednisolone from 1 mg to 2 mg per kilogram per day orally, and budesonide from 0.25 mg to 0.5 mg twice daily), and azithromycin was begun. Supplemental oxygen was gradually weaned. The patient was discharged on the ninth day, receiving prednisolone (to taper over a period of 1 week) and azithromycin (total, 5-day course); albuterol, budesonide, and sodium chloride were given by nebulizer. His mother was encouraged to stop smoking.

At the ages of 7, 7.5, and 9 months, the patient was again admitted to the hospital because of fever and respiratory distress. When he was 7.5 months of age, testing for influenza A virus antigen was positive (H1N1 presumed), and when he was 9 months of age, testing for respiratory syncytial virus was positive. On physical examination, there were persistent fine crackles in both lungs. Each time, his condition improved with supportive care, and he was discharged after 5 to 7 days.

When the patient was 9 months of age, computed tomography (CT) of the chest performed after the intravenous administration of contrast material revealed bilateral, symmetric paramediastinal ground-glass opacities, with scattered regions of air trapping, areas of atelectasis in the dependent portions of the lungs, and a few small parenchymal nodules. Chest radiographs taken 2 weeks later showed hyperinflated lungs and increasing perihilar patchy opacities in the right lung.

One month later, a diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

Dr. T. Bernard Kinane: May we review the chest radiographs?

Dr. Randheer Shailam: Obtained at the time of the first admission, a frontal chest radiograph shows bilateral patchy perihilar opacities (Fig. 1A) and a lateral chest radiograph shows flattening of the hemidiaphragms, indicating hyperinflation (Fig. 1B). These findings can be seen in cases of reactive airway disease, atypical pneumonia, or bronchiolitis.

Dr. Kinane: I am aware of the diagnosis in this case. This 9-month-old infant had recurring respiratory distress that began when he was 5 months of age. There are no dysmorphic features, and the infant is growing normally. The findings on auscultation — namely, rhonchi with persistent fine crackles in the background — are unusual. The chest radiograph shows persistent hyperinflation and an absence of parenchymal infiltrates. The disease in this case seems to be confined to the respiratory system; there seems to be no cardiac abnormality. Since the child is growing well, an underlying immunodeficiency is unlikely.

REACTIVE AIRWAY DISEASE

Recurrent wheezing is not unusual in infants and can be seen in up to 19% of children.[1] It has many names, including reactive airway disease and transient early wheeze. The underlying cause is the

small airways of infants.[1] When a respiratory tract infection develops in an infant, the diameter of the lumen becomes even smaller and the child wheezes. Reactive airway disease gradually resolves during early childhood. The resolution is thought to be related to growth of the airways. The most characteristic findings in this condition are recurrent wheeze and hyperinflation, and this infant has these findings. However, he had persistent fine crackles on physical examination and prolonged periods of hypoxemia, a pattern that is not consistent with reactive airway disease.

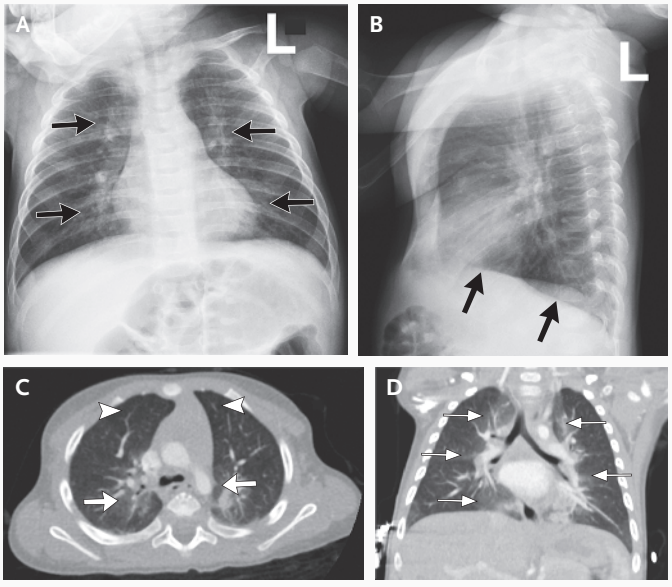

Figure 1. Imaging Studies.
A frontal chest radiograph obtained when the patient was 5.5 months of age shows patchy perihilar opacities (Panel A, arrows); a lateral chest radiograph obtained at the same time shows flattening of the hemidiaphragms, indicating hyperinflation (Panel B, arrows). An axial CT scan at the level of the carina shows centrally distributed ground-glass opacities bilaterally (Panel C, arrows) and areas of low attenuation anteriorly (arrowheads), indicating air trapping. Coronal reformatted CT images depict the central ground-glass opacities involving all zones (Panel D, arrows).

INTERSTITIAL LUNG DISEASE

The findings in this patient are consistent with interstitial lung disease. In pediatric patients, a diagnosis of interstitial lung disease is considered when the child has tachypnea, persistent fine crackles, and hypoxemia.[2] Wheezing occurs in 20% of patients with pediatric interstitial lung disease, and most cases start with a viral illness,[2] as in this patient. The estimated incidence is 0.36 cases per 100,000 children, and there is a male predominance (60:40).[3] Three quarters of cases of interstitial lung disease in children are manifested before the patient is 1 year of age, as in this child, with a median age at onset of 8 months.[2,3] In almost 20% of pediatric cases, there is a family history of interstitial lung disease. This patient has a family history of asthma, but not of interstitial lung disease.

Adult-Type Interstitial Lung Disease

In adults with interstitial lung disease, there are three main patterns — usual interstitial pneumonitis, nonspecific interstitial pneumonitis, and lymphoid interstitial pneumonitis.[4] Usual interstitial pneumonitis is characterized by alteration of the pulmonary architecture due to fibrosis. It is the most common adult form of interstitial lung disease, with onset in the fifth decade. Many cases have been described in pediatric patients, but these cases do not have the typical fibroblastic foci and therefore may represent other diseases.[5,6] Nonspecific interstitial pneumonitis has less scarring and a better prognosis than usual interstitial pneumonitis; it is generally not seen in infants but has been described in the context of a mutant ATP-binding cassette (ABC) transporter A3 protein (ABCA3).[7] Approximately 6% of children with interstitial lung disease have lymphoid interstitial pneumonitis, which is seen almost exclusively in the context of autoimmune disease and immunodeficiencies.[8,9] This child is growing normally, so immunodeficiency is unlikely, and therefore, lymphoid interstitial pneumonitis is an unlikely diagnosis. We can conclude that this child's condition is most likely not attributable to adult-type interstitial lung disease.

Childhood Interstitial Lung Disease

The classification of interstitial lung diseases in children differs from their classification in adults. In children, these disorders are classified on the basis of the primary location of the disease — the airway, the alveolus, or the interstitium (Table 1). Defects in development and in the surfactant pathways are important considerations in the pathophysiology.[5,10]

DISEASES OF THE AIRWAY

Diseases of the airway are characterized by crackles and rhonchi on auscultation, hyperinflated lungs on chest radiography, and a CT scan that

Table 1. Classification of Pulmonary Diseases in Children According to Anatomical Location in the Lung.

Airway
Persistent tachypnea of infancy, or neuroendocrine-cell hyperplasia of infancy
Follicular bronchitis
Bronchocentric granulomatosis
Bronchiolitis obliterans
Interstitium
Nonspecific interstitial pneumonitis (increased numbers of fibroblasts and lymphocytes)
Cellular interstitial pneumonitis, or pulmonary interstitial glycogenosis (increased numbers of mesenchymal cells)
Lymphocytic interstitial pneumonitis (increased numbers of lymphocytes)
Alveolus
Pulmonary alveolar proteinosis
Mutations in the surfactant pathway
Chronic pneumonitis of infancy

shows a nonhomogeneous pattern, with some areas of hyperinflation and some areas of hypoinflation. This patient had findings on examination and chest radiography that suggest airway disease. Specific diagnoses include persistent tachypnea of infancy associated with neuroendocrine-cell hyperplasia of infancy (NEHI), follicular bronchitis, bronchocentric granulomatosis, and bronchiolitis obliterans.

Neuroendocrine-Cell Hyperplasia of Infancy and Follicular Bronchitis

When persistent tachypnea of infancy was first described, the lung-biopsy specimens were thought to be normal; later, however, neuroendocrine-cell hyperplasia in small airways was recognized.[11-14] Most cases occur in full-term infants. The onset of fine crackles and hypoxemia usually occurs at 4 months of age, close to the age of this patient at first presentation. In pediatric follicular bronchitis, lymphoid follicles obstruct the airway; infants with this condition have an average age at presentation of 6 weeks.[15] The prognoses of patients with NEHI and follicular bronchiolitis are excellent. These two conditions may be the same entity, with different morphologic features depending on whether there is a preceding or concurrent viral infection.

Bronchocentric Granulomatosis and Bronchiolitis Obliterans

Bronchocentric granulomatosis is a theoretical consideration in this patient. The disease is characterized by granulomatous inflammation involving the small airways. It has been described in children, but not in infants. Fifty percent of patients with bronchocentric granulomatosis also have asthma. The findings on CT scanning are characteristic of bronchocentric granulomatosis. Bronchiolitis obliterans is also a consideration and is seen in the pediatric population.[16] In most cases, there is an obvious cause, such as a connective-tissue disorder or an infection, particularly adenoviral infection. On rare occasions, cases are seen after bone marrow or lung transplantation or in association with toxic epidermal necrolysis.

CELLULAR INTERSTITIAL PNEUMONITIS

Cellular interstitial pneumonitis (also called pulmonary interstitial glycogenosis) is another pediatric lung disease to consider. Patients present in infancy with tachypnea and pulmonary infiltrates, without hyperinflation.[17] There is an interstitial pattern on chest radiographs and an alveolar pattern on CT. The disease is characterized by small cells in the interstitium, which are mesenchymal in origin and are rich in glycogen.[18] Cellular interstitial pneumonitis is unlikely in this patient because the radiographs showed hyperinflation.

MUTATIONS IN THE SURFACTANT PATHWAY

Mutations in the genes encoding the proteins that make up the surfactant pathway can lead to childhood interstitial lung disease, which has a characteristic pattern on examination of the biopsy specimen, resembling that seen in desquamative interstitial pneumonia in adults; the condition has been called chronic pneumonitis of infancy. During the past 10 years, mutations in key components of the surfactant pathways have been found in this condition, including the genes encoding surfactant protein B (*SP-B*), surfactant protein C (*SP-C*), and the transporter ABCA3.[10] Mutations in *SP-B* are inherited in an autosomal recessive pattern and are characterized by a severe phenotype involving the onset of respiratory distress during the first few days of life. Mutations in *SP-C* are inherited in an autosomal dominant pattern and are clinically less severe. Mutations in *ABCA3* also result in intersti-

tial lung disease and have an autosomal recessive pattern of inheritance. The clinical presentation is highly variable, with hypoxemia, infiltrates on the chest radiograph, septal thickening, and hypoinflation of the lungs. The CT scan shows a ground-glass pattern that probably indicates the accumulation of material in the alveolus. This patient's imaging and clinical findings as well as the lack of a family history argue against mutations in the surfactant pathway.

DEVELOPMENTAL DEFECTS

Diffuse lung diseases that present in infancy are listed in Table 2. In addition to the diagnoses already discussed, defects in development must be considered, including acinar dysplasia, congenital alveolar dysplasia, and alveolar capillary dysplasia. These disorders result from defects in the formation of the alveolus, with or without defects in the alignment of blood vessels. Since the alveolus is central to gas exchange, these conditions are severe and usually are manifested at birth with severe respiratory distress and hypoxemia.

Lung hypoplasia is another general defect in lung development that can occur. Distention of the lung prenatally and fetal breathing are necessary for lung development. Lung hypoplasia occurs when the volume of amniotic fluid is reduced, as in Potter's syndrome. Also, defects in the chest wall that limit lung expansion, such as diaphragmatic hernia, can result in lung hypoplasia. Reduced intrauterine respiratory movements can result in hypoplasia, and such a reduction is seen in many muscular and neurologic conditions, such as spina bifida and spinal muscular atrophy. None of these developmental defects appear likely in this otherwise well 9-month-old infant.

May we review the chest CT?

Dr. Shailam: The CT scan of the chest shows central areas of ground-glass opacities involving all lobes, as well as areas of low attenuation, indicating air trapping. At the level of the carina (Fig. 1C), there are perihilar areas of ground-glass opacities bilaterally and air trapping in the anterior portions of the lungs. No septal or pleural thickening, no pleural fluid, and no enlarged lymph nodes are present. Coronal reformatted images of the same data (Fig. 1D) show centrally distributed ground-glass opacities, as well as areas of air trapping. These findings are suggestive of NEHI.

Table 2. Diffuse Lung Diseases That Occur in Infancy.

Developmental disorders related to defects in alveolar formation (usually severe)
Acinar dysplasia
Congenital alveolar dysplasia
Alveolar capillary dysplasia
Pulmonary hypoplasia
Disorders of unknown cause (favorable course)
Cellular interstitial pneumonitis, or pulmonary interstitial glycogenosis
Persistent tachypnea of infancy, or neuroendocrine-cell hyperplasia of infancy
Defects in surfactant metabolism (usually severe)
Mutations in the genes encoding surfactant protein B, surfactant protein C, and ATP-binding cassette transporter A3

Dr. Kinane: On examination, this 9-month-old boy with persistent respiratory distress was found to have fine crackles; therefore, he has interstitial lung disease. The hyperinflation of the lungs suggests that he has a disorder of small airways. Because he looks so well, follicular bronchitis and NEHI are the most plausible diagnoses. The two conditions may be part of the same spectrum. The infant presented at the age of 5 months, which suggests NEHI. Defects in the immune system, lung development, or surfactant metabolism are unlikely in this case.

The diagnostic procedure was a lung biopsy.

DR. T. BERNARD KINANE'S DIAGNOSIS

Neuroendocrine-cell hyperplasia of infancy (NEHI).

PATHOLOGICAL DISCUSSION

Dr. Eugene J. Mark: A wedge biopsy of the lung was performed at thoracoscopy. Examination of the specimen revealed normal alveoli, but the bronchioles appeared prominent because of epithelial thickening (Fig. 2A). Closer inspection revealed that a portion of the thickening was due to a layer of clear cells along the basement membrane (Fig. 2B). This layer was historically termed "the clear-cell organ" but is now known to be composed of neuroendocrine cells. Depending on the region of the bronchiole, these clear cells either formed small nests

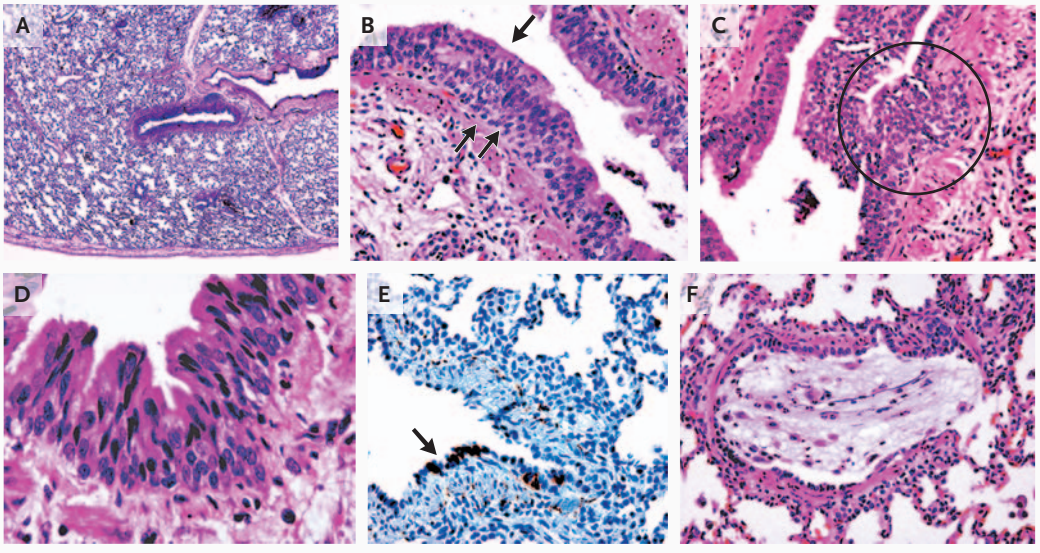

Figure 2. Lung-Biopsy Specimen.

The bronchioles appear prominent at low magnification (Panel A, hematoxylin and eosin) because the epithelium is hypercellular. At higher magnification, a layer of clear cells, historically described as the clear-cell organ of neuroendocrine cells (Panel B, arrows; hematoxylin and eosin), is evident between the columnar ciliated epithelium and the basement membrane (paired arrows). A nest of neuroendocrine cells (encircled in Panel C, hematoxylin and eosin) is present between smooth muscle and the lumen of the bronchiole. A papillary proliferation of columnar epithelial cells is superimposed on increased numbers of neuroendocrine cells (Panel D, hematoxylin and eosin). Immunohistochemical staining for synaptophysin (Panel E, immunoperoxidase) shows that neuroendocrine cells stain in a continuous linear array in the bronchial epithelium (arrow). A bronchiole is filled with mucus and scattered eosinophils (Panel F, hematoxylin and eosin), a finding consistent with infection or asthma.

(Fig. 2C) or were more evenly distributed. These clear cells are the defining histopathological feature of NEHI.[13,14] There was also papillary proliferation of the respiratory epithelial cells (Fig. 2D). Immunochemical staining to confirm the neuroendocrine nature of the cells showed that the number of cells in many bronchioles was increased (Fig. 2E) as compared with the isolated and scattered neuroendocrine cells seen in the normal lung. In addition, some bronchioles were plugged with mucus and scattered eosinophils (Fig. 2F), a finding consistent with either infection or asthma.

There is a spectrum of neuroendocrine proliferations in the lungs in adults (Table 3). Most of these conditions are not seen in infants and children, and the diffuse forms of neuroendocrine-cell hyperplasia in adults constitute an underrecognized spectrum of disease.[19-21] For the surgical pathologist, it is easy to overlook diffuse neuroendocrine-cell hyperplasia in both adults and infants because neuroendocrine cells are smaller than respiratory epithelial cells, have clear cytoplasm, and may be arrayed linearly or erratically in the bronchioles. An increased number of neuroendocrine cells is diagnostic of NEHI, and there is a relationship between the visibility of neuroendocrine cells and the severity of small-airway obstruction seen on pulmonary-function testing.[14] The CT findings in infants with persistent tachypnea[22] can prompt the pathologist to quantitate the neuroendocrine cells.

NEHI has been reported to be familial.[23] Children with neuroendocrine hyperplasia have been reported to have normal levels of KL-6, a glycoprotein secreted by type II alveolar pneumocytes, in contrast to children with inborn errors of surfactant metabolism.[24] To my knowledge, the degree of columnar epithelial proliferation seen in this case has not been reported previously. It is possible that this proliferation represents a reaction to infection or inflammation.

DISCUSSION OF MANAGEMENT

Dr. Kinane: What are the implications of this diagnosis for this child? The long-term outcome among patients with this disease is usually excellent. No child is known to have died from NEHI,[13] and in most children, the condition gradually improves during the first 4 years of life. Their respiratory reserve may be low, and they are frequently admitted to the hospital with respiratory tract infections and exacerbations during the first few years of life; they may have mild, intermittent exercise intolerance and intermittent wheezing and crackles on examination. Pulmonary-function testing after 5 years of age is normal in most children, but for some patients, test results show decreased small-airway flow and increased residual volume.

NEHI is a rare disease, and to my knowledge, no clinical trials to establish the best therapeutic regimen have been conducted. Supportive therapies such as the administration of supplemental oxygen and nutrition are critical. Therapeutic interventions, such as the administration of anti-inflammatory medications, hydroxychloroquine, and intravenous immune globulin, have led to partial responses.[13,15] However, most children with NEHI receive a therapeutic trial of systemic glucocorticoids.

Dr. Tse: The patient was readmitted at 11 months of age with adenovirus infection. Because of his repeated admissions, we began treatment with hydroxychloroquine (10 mg per kilogram per day) and twice-daily inhaled budesonide. There was clinical improvement during the next few months; although he continued to have viral upper respiratory infections, they did not require hospitalization. Because of an exacerbation when he was 22 months of age, we added azithromycin to the regimen three times weekly. His mother reported that the patient seemed better after starting azithromycin, so we continued this. When the patient was 2 years of age, his mother reported that it was difficult to administer the hydroxychloroquine because of its bad taste. Since the patient was doing well, she discontinued all his medications at that time.

At follow-up 3 months later, when he was 27 months of age, the patient had had no further exacerbations and had not been hospitalized in more than a year. However, his oxygen saturation, which was 95% at rest while he was breathing ambient air, decreased to 90% on exertion, with a respiratory rate at rest of 32 breaths per minute, some subcostal retraction, and fine crackles on chest auscultation. The administration of azithromycin was restarted, and we will continue to follow him closely.

Table 3. Neuroendocrine Proliferations in the Lung in Adults.

Diffuse neuroendocrine hyperplasia (i.e., an aggregation or a linear presentation of neuroendocrine cells)
Carcinoid tumorlet (i.e., a nodular proliferation of neuroendocrine cells [>5 mm] breaching the basement membrane)
Carcinoid tumor
Atypical carcinoid tumor (>10 mitoses per high-power field and necrosis)
Small-neuroendocrine-cell carcinoma
Large-neuroendocrine-cell carcinoma
Fetal adenocarcinoma of the lung (blastoma)
Combined adenocarcinoma and neuroendocrine carcinoma

Dr. Mark: This child does not have bronchiolitis obliterans or constrictive bronchiolitis because the bronchioles that we see are not obviously obliterated or constricted. The columnar mucinous cells and the neuroendocrine cells have caused narrowing of the bronchiolar lumens. Whether the columnar metaplasia is related to an infection or to the increase in neuroendocrine cells is unclear. There is minimal interstitial disease.

Dr. Kinane: There is a report that neuroendocrine cells can secrete growth factors that contribute to lung growth and development.[25] The number of neuroendocrine cells is increased in bronchopulmonary dysplasia, a condition that is characterized by airway disease. We do not know whether the neuroendocrine cells are markers of injury or are an important component of disease pathogenesis.

ANATOMICAL DIAGNOSIS

Neuroendocrine-cell hyperplasia of infancy (NEHI).

This case was discussed at the postgraduate course "Thoracic Pathology — Current Concepts," sponsored by Massachusetts General Hospital and the Harvard Medical School Department of Continuing Education.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. N Engl J Med 1995;332:133-8.
2. Deutsch GH, Young LR, Deterding RR, et al. Diffuse lung disease in young children: application of a novel classification scheme. Am J Respir Crit Care Med 2007;176:1120-8.
3. Dinwiddie R, Sharief N, Crawford O. Idiopathic interstitial pneumonitis in children: a national survey in the United Kingdom and Ireland. Pediatr Pulmonol 2002;34:23-9.
4. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment: international consensus statement. Am J Respir Crit Care Med 2000;161:646-64.
5. Fan LL, Deterding RR, Langston C. Pediatric interstitial lung disease revisited. Pediatr Pulmonol 2004;38:369-78.
6. Langston C, Fan LL. Diffuse interstitial lung disease in infants. Pediatr Pulmonol 2001;23:Suppl:74-6.
7. Young LR, Nogee LM, Barnett B, Panos RJ, Colby TV, Deutsch GH. Usual interstitial pneumonia in an adolescent with ABCA3 mutations. Chest 2008;134:192-5.
8. Church JA, Isaacs H, Saxon A, Keens TG, Richards W. Lymphoid interstitial pneumonitis and hypogammaglobulinemia in children. Am Rev Respir Dis 1981;124:491-6.
9. Joshi VV, Oleske JM, Minnefor AB, et al. Pathologic pulmonary findings in children with the acquired immunodeficiency syndrome: a study of ten cases. Hum Pathol 1985;16:241-6.
10. Nogee LM. Genetics of pediatric interstitial lung disease. Curr Opin Pediatr 2006;18:287-92.
11. Brody AS, Crotty EJ. Neuroendocrine cell hyperplasia of infancy (NEHI). Pediatr Radiol 2006;36:1328.
12. Deterding RR, Fan LL, Morton R, Hay TC, Langston C. Persistent tachypnea of infancy (PTI) — a new entity. Pediatr Pulmonol 2001;23:Suppl:72-3.
13. Deterding RR, Pye C, Fan LL, Langston C. Persistent tachypnea of infancy is associated with neuroendocrine cell hyperplasia. Pediatr Pulmonol 2005;40:157-65.
14. Young LR, Brody AS, Inge TH, et al. Neuroendocrine cell distribution and frequency distinguish neuroendocrine cell hyperplasia of infancy from other pulmonary disorders. Chest 2011;139:1060-71.
15. Kinane BT, Mansell AL, Zwerdling RG, Lapey A, Shannon DC. Follicular bronchitis in the pediatric population. Chest 1993;104:1183-6.
16. Moonnumakal SP, Fan LL. Bronchiolitis obliterans in children. Curr Opin Pediatr 2008;20:272-8.
17. Schroeder SA, Shannon DC, Mark EJ. Cellular interstitial pneumonitis in infants: a clinicopathologic study. Chest 1992;101:1065-9.
18. Canakis AM, Cutz E, Manson D, O'Brodovich H. Pulmonary interstitial glycogenosis: a new variant of neonatal interstitial lung disease. Am J Respir Crit Care Med 2002;165:1557-65.
19. Davies SJ, Gosney JR, Hansell DM, et al. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia: an underrecognised spectrum of disease. Thorax 2007;62:248-52.
20. Ge Y, Eltorky MA, Ernst RD, Castro CY. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. Ann Diagn Pathol 2007;11:122-6.
21. Koo CW, Baliff JP, Torigian DA, Litzky LA, Gefter WB, Akers SR. Spectrum of pulmonary neuroendocrine cell proliferation: diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, tumorlet, and carcinoids. AJR Am J Roentgenol 2010;195:661-8.
22. Brody AS, Guillerman RP, Hay TC, et al. Neuroendocrine cell hyperplasia of infancy: diagnosis with high-resolution CT. AJR Am J Roentgenol 2010;194:238-44.
23. Popler J, Gower WA, Mogayzel PJ Jr, et al. Familial neuroendocrine cell hyperplasia of infancy. Pediatr Pulmonol 2010;45:749-55.
24. Doan ML, Elidemir O, Dishop MK, et al. Serum KL-6 differentiates neuroendocrine cell hyperplasia of infancy from the inborn errors of surfactant metabolism. Thorax 2009;64:677-81.
25. Aguayo SM, Schuyler WE, Murtagh JJ Jr, Roman J. Regulation of lung branching morphogenesis by bombesin-like peptides and neutral endopeptidase. Am J Respir Cell Mol Biol 1994;10:635-42.