Allergic rhinitis and asthma in a patient with unilateral pulmonary agenesis

Melinda M. Rathkopf, MD*; Diane Napoli, MD*; and Jeffrey G. Walls, MD†

CHIEF COMPLAINT

Chronic cough and nasal symptoms in a patient with unilateral pulmonary agenesis.

MEDICAL HISTORY

History of Present Illness

A 23-year-old woman presented to the allergy/immunology clinic with a previous diagnosis of allergic rhinitis and asthma. The patient reported that she had started immunotherapy (IT) 34 weeks ago, prescribed by her prior allergist, and had been receiving IT at her college health clinic. Following graduation 2 months earlier, she had been giving herself IT injections at home. She denied any reactions and had injectable epinephrine available at home. She was new to our area and was interested in restarting her IT. Her nasal symptoms included congestion, rhinorrhea, sneezing, itching, and postnasal drip. She also complained of ocular watering, itching, injection, and discharge when around cats or dogs. Chest symptoms included a daily cough and occasional wheezing that she did not notice but others had pointed out to her. She denied any nocturnal symptoms. She had an albuterol metered-dose inhaler available but had not used it in the previous 3 months.

Past Medical History

The only medical record available was a single clinic note from her prior allergist. Noted medical problems included unilateral pulmonary agenesis, moderate persistent asthma, and perennial allergic rhinitis with seasonal exacerbation. Her pulmonary agenesis was diagnosed at 6 months of age during an upper respiratory tract infection during which she turned blue by the patient's report. There were neither childhood medical records available for review nor comments about childhood medical history noted by her prior allergist.

She was diagnosed as having asthma in early childhood and treated in an emergency department once for her asthma but does not recall any hospitalizations. She denied any admission to the intensive care unit or intubation. Her medications on presentation included inhaled budesonide (200 μg per spray Turbuhaler), 2 puffs twice a day, and inhaled pirbuterol (0.2 mg per spray Autohaler), 1 to 2 puffs as needed. Spirometric values from her prior allergist were a forced expiratory volume in 1 second (FEV_1) of 1.10 L (35% predicted), forced vital capacity (FVC) of 2.12 L (58% predicted), and an FEV_1/FVC ratio of 0.52. These findings were consistent with the results of pulmonary function tests obtained on prior visits with her previous allergist.

The patient stated that she had allergic rhinitis symptoms since childhood and had undergone IT for a few years starting at approximately 9 years of age. She felt that IT improved her allergic rhinitis symptoms. She restarted IT in 2001 and continued for 34 weeks, when she graduated from college, was married, and then moved to her current location. Her most recent allergy medications included nasal budesonide, 1 spray per nostril each morning, and cetirizine, 10 mg at bedtime.

Past Surgical History

Per patient report, her past surgical history is significant for aortopexy that was performed to relieve obstruction of the left mainstem bronchus and left breast augmentation.

Family History

Her family history was significant only for her father, who had asthma and allergic rhinitis.

Physical Examination

On examination, the patient was a slender, white woman in no acute distress. Her pulse oximetry was 98% on room air, and she spoke in complete sentences. Her conjunctiva were mildly injected without discharge. She had mild postpharyngeal cobblestoning, and her nasal mucosa was erythematous with minimal clear discharge. There was no evidence of edematous pale turbinates or polyps, no cervical adenopathy, no pectus or other notable external chest deformity, and no obvious scarring from previous surgical procedures. Her lung sounds were greater on the left than right side, with poor basilar air movement. No wheezing was noted, but a resonating, tubular sound was heard on forced expiration. Cardiac

* Department of Allergy/Immunology, Wilford Hall Medical Center, Lackland AFB, Texas.
† Department of Pulmonary Medicine, Wilford Hall Medical Center, Lackland AFB, Texas.
The views expressed in this article are those of the authors and do not represent the official policy or position of the United States Air Force, the Department of Defense, or the United States Government.
Received for publication June 24, 2003.
Accepted for publication in revised form September 30, 2003.

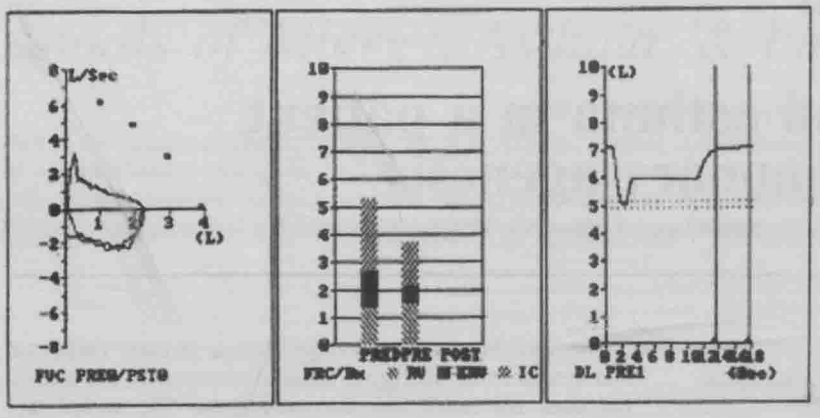

Figure 1. The flow-volume loop (FVL) obtained from the patient is similar to that seen in patients with obstructive ventilatory patterns. The linear descent of the FVL is disrupted by an initial sharp downward deflection. This is thought to be due to compression of the major central airways (tracheobronchial collapse).[4]

examination revealed displacement of heart sounds to the right. Her skin examination results were normal.

LABS/Laboratory and Radiology Findings

The patient was skin prick tested to our standard adult panel of 43 antigens, including outdoor and indoor aeroallergens. Spirometry was performed immediately before skin testing, and the results were consistent with the patient's baseline levels. She was asymptomatic and believed to be stable for skin prick testing. Intradermal skin testing was not performed because of the increased risk of immediate systemic reactions associated with intradermal skin testing.[1] Her skin test results were positive for *Dermatophagoides pteronyssinus,* with appropriate good controls. Her pulmonary function test results (Fig 1) were significant for an FVC of 2.16 L (56% predicted), FEV_1 of 1.34 L (43% predicted), FEV_1/FVC ratio of 0.62, and a forced expiratory fraction at 25% to 75% of 0.96 L (26% predicted). Her vital capacity was 2.13 L (55% predicted), and her total lung capacity was 3.63 L (69% predicted), with a residual volume of 1.50 L (105% predicted) and a ratio of residual volume to total lung capacity of 0.41. Her diffusion capacity of carbon monoxide was 17.25 mL/mm Hg per minute (75% predicted), with a diffusion capacity adjusted for alveolar ventilation of 6.26 (144% predicted). Her chest computed tomogram (CT; Fig 2) showed right posterior shift of the heart and mediastinum. The right main stem bronchus appeared to end in a blind pouch with no evidence of right pulmonary parenchyma. The trachea was enlarged. The left lung was hyperexpanded, with the left upper lobe located within the right hemithorax and the left lower lobe in the left hemithorax. Her echocardiogram was significant only for rightward shift of her heart; no other cardiac abnormalities were present, and her ejection fraction was 60% to 65%.

Clinical Course and Management

Our patient was clinically diagnosed as having asthma in early childhood. No medical records were available to elaborate on her symptoms. She complained of a chronic cough but rarely, if any, wheezing. She rarely used albuterol. Her baseline spirometry results in our clinic were clearly abnormal, as would be expected with her underlying defect. The FEV_1/FVC ratio of 0.62 was lower than expected from a pure absence of one lung. She demonstrated a 9% (110-mL) improvement in FEV_1 after albuterol nebulization in our clinic. Despite treatment with moderate- to high-dose inhaled corticosteroids in the past, her spirometry values were essentially unchanged from those obtained from her prior allergist. She was believed to be a poor candidate for challenge testing due to an FEV_1 of 1.14 L (36% predicted).

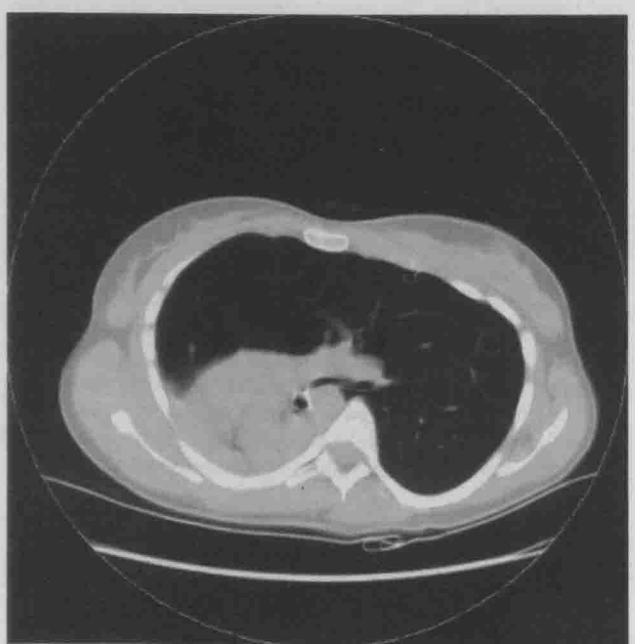

Figure 2. Computed tomogram demonstrating left lung hyperexpansion with displacement of the heart to the right side. The right main stem bronchus ends in a blind pouch, and the left main stem bronchus courses anterior to the descending aorta.

Administration of IT at home was stopped on presentation to the allergy clinic. In accordance with the clinical guidelines set forth by the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology, IT should be administered under the supervision of an appropriately trained physician and personnel, and patients at high risk should receive IT under the supervision of the prescribing allergist.[2] Because of her significant comorbid condition, the patient did not continue immunotherapy, and conservative medical management was chosen for her perennial allergic rhinitis. Because she was monosensitized to house dust mites, she was educated on dust mite allergies and avoidance measures and prescribed cetirizine and fluticasone nasal spray. She started using fluticasone and salmeterol and was referred to the pulmonary medicine department.

Referral to the pulmonary medicine department yielded the impression of right pulmonary aplasia (unilateral pulmonary agenesis type 2) and airflow obstruction. The obstruction could be due to asthma vs mechanical distortion of the left mainstem bronchus. The pulmonologist agreed that she was not a candidate for bronchoprovocation given her severe baseline obstruction. The patient reported symptom improvement while taking fluticasone and salmeterol, and the pulmonologist recommended continued use of these medications and following up the patient clinically.

QUESTION

Does This Patient Have Asthma?

The typical symptoms of asthma are wheezing, cough, chest tightness, shortness of breath, and sputum production. The diagnosis of asthma is suggested if symptoms are variable and nocturnal; triggered by cold air, exercise, or known allergen; and improve with standard asthma medications.[3] The diagnosis is well supported by demonstration of airflow obstruction with reversibility. In patients with baseline airflow obstruction, more than a 12% increase with a 200-mL improvement in FEV_1 after use of an inhaled β_2-agonist confirms the diagnosis.[4] If bronchodilator reversibility is inconclusive, a trial of corticosteroids followed by repeat spirometry can also be used to demonstrate reversibility. Peak expiratory flow rate (PEFR) variability can suggest a diagnosis of asthma in patients with normal spirometry results and lack of diagnostic reversibility. PEFR is measured on rising in the morning before inhaled β_2-agonist use and then after inhaled β_2-agonist use in the afternoon, with a 20% difference between measurements suggestive of asthma.[5]

Evidence of airway hyperresponsiveness can also support the diagnosis of asthma in the appropriate clinical setting. Bronchoprovocation with methacholine or histamine can be used to test for nonspecific airway hyperresponsiveness. Challenge testing is an option when asthma is a diagnostic possibility and prebronchodilator and postbronchodilator spirometry is not significant. Challenge testing is, however, more useful in excluding than in establishing the diagnosis of asthma, since the negative predictive power is greater than the positive predictive power.[4] Unfortunately, bronchoprovocation is not without risk. According to the American Thoracic Society, severe airflow limitation, defined as an FEV_1 of less than 50% predicted or less than 1.0 L, is an absolute contraindication for bronchoprovocation, whereas moderate airflow limitation (FEV_1 <60% predicted or <1.5 L) is a relative contraindication.[4] Full pulmonary function tests can be beneficial in the evaluation and differentiation of asthma from other processes. Patients with obstructive lung disease such as asthma often have an increased residual volume. Diffusion capacity is usually normal or increased in asthma; a reduced diffusion capacity should prompt a search for alternate diagnoses.[6]

DISCUSSION

Pulmonary agenesis is a rare congenital malformation of the lung that is found in only 1 of every 10,000 to 15,000 autopsies and has been estimated at approximately 1 in 15,000 live births.[7,8] Different individuals have been credited with the initial description. The earliest reference is thought to be by DePozze in 1673, who observed it unintentionally during an autopsy of a young woman.[9] However, others attribute the first description to Morgagni in 1762[7] or Klebs in 1874.[8] Munchmeyer first diagnosed unilateral agenesis of the lung clinically in 1885.[10] From 1937 to 1997, there were 269 cases reported in the literature.[11] Unilateral agenesis seems to affect both sides of the lung equally and has no sex predilection. The malformation is classified by extent of the defect. Schneider and Schwalbe[12] established an initial classification scheme. Group 1 included those with complete absence of the lung and bronchus, group 2 had no evidence of any lung tissue but had a bronchus that ended in a blind pouch, and group 3 had an essentially normal bronchus that ended in a fleshy structure. Boyden[13] proposed a more complete classification scheme. Type 1 was pure agenesis with complete absence of one or both lungs; type 2 had aplasia with suppression of all but a rudimentary bronchus; type 3 had abortive growth or hypoplasia.[14]

Lung formation begins during the embryonic period at approximately 22 to 26 days of gestation with a ventral outpouching of the primitive foregut into the surrounding tissue. This early lung bud develops into the trachea, bronchi, and other conducting airways and gas-exchanging units. During the next few days, this bud divides into right and left units that eventually become the right and left mainstem bronchus. During the next 2 weeks, branching continues until the primitive lung is formed by the end of the seventh week of gestation.[15] Pulmonary agenesis and aplasia occur during this period. The earlier the arrest occurs in the development of a lobe or lung, the more severe the defect will be. The bronchial arteries appear to supply the newly developing lung tissue. Failure of angiogenesis to the lung bud has been proposed as an origin of pulmonary agenesis. A genetic basis for pulmonary agenesis has been proposed, but results are controversial.[10] Unilateral pulmonary agenesis has been reported in

association with a 22q11.2 deletion in a patient with the manifestation of velocardiofacial syndrome. This association was thought to be due to the migration of neural crest cells in the development of the aortic arch.[16] There are also 2 reports in the literature of patients with pulmonary agenesis and partial duplication of chromosome 2.[17] There are multiple causes of hypoplasia, including vascular abnormalities and tracheobronchial tree obstruction.[8] Approximately half of the cases of pulmonary agenesis have associated anomalies. Table 1 lists the more commonly associated congenital anomalies.[18-20]

The clinical presentation varies and usually depends on the presence of the coexistent anomalies. Less typically, patients may be asymptomatic, and the diagnosis is surreptitiously made on routine chest x-ray examination obtained for other reasons. Others are symptomatic early and present with recurrent pulmonary infections or respiratory distress. Symptoms may include dyspnea, wheezing, tachypnea, and cyanosis on exertion.[21] Early cyanosis or respiratory distress usually implies the coexistence of a major congenital heart lesion, but only approximately 20% of cases have cyanosis at birth. Physical examination findings depend on which lung is absent and also whether there is dextrocardia in the case of absence of the right lung. Although the chest initially has a normal shape, lack of growth on the affected side can make chest asymmetry more pronounced in an adult. An absence of breath sounds on the affected side would be expected, but this is usually not the case, since the empty hemithorax is filled with herniated normal lung such that anterior breath sounds are heard on the affected side but not the axillary or basilar sides. A diagnostic approach has been recommended, beginning with a plain chest x-ray examination. A plain film will usually show complete opacification of the hemithorax with mediastinal shift to the affected side. With the absence of the right lung, there is an apparent dextrocardia. Ribs on the affected side may be closer together, and 13 pair of ribs is not an uncommon feature. Second-line imaging usually consists of CT scan or ultrasonography. CT scan may reveal a fully opacified hemithorax without visualization of the main bronchus. Ultrasound with Doppler echocardiography can show the course of the pulmonary artery. Bronchoscopy has been considered the "gold standard" but may not always be necessary. It may show the absence of the carina or one of the mainstem bronchi in pulmonary agenesis or a blind pouch in pulmonary aplasia. It may also reveal evidence of an associated tracheoesophageal fistula. Angiobronchography can be used to show the absence of the pulmonary artery and bronchus. Electrocardiography is only useful when dextrocardia is present. Once the diagnosis is established, additional studies, including echocardiography, renal ultrasound, and barium swallow, can be used to look for associated anomalies.[22]

Table 1. Congenital Anomalies Associated with Pulmonary Agenesis

System	Anomalies
Cardiovascular	Patent ductus arteriosus
	Transposition of the great arteries
	Atrial septal defect
	Ventricular septal defect
	Patent foramen ovale
Gastrointestinal	Tracheoesophageal fistula
	Duodenal atresia
	Annular pancreas malrotation
	Meckel diverticulum
	Imperforate or ectopic anus
Skeletal	Hemivertebra/rib anomalies
	Spina bifida
	Scoliosis
	Thumb hypoplasia
	Metacarpal and radial anomalies
Genitourinary	Absent kidney
	Horseshoe kidney
	Abnormal ureter placement
	Unicornate uterus
	Double uterus and vagina
Miscellaneous	Hemifacial macrosomia
	Malocclusion
	Cleft lip and palate
	Hydrocephalus
	Accessory diaphragm
	Microphthalmia

The medical literature regarding lung function in patients with unilateral pulmonary agenesis is limited. In a 1967 review article by Booth and Berry,[14] spirometry was performed in 7 of their 8 patients. All 7 patients demonstrated significant reduction in both FEV_1 and FVC, but 6 had a normal FEV_1/FVC ratio, suggesting only a reduction in total lung volume. The one abnormal FEV_1/FVC ratio was 0.69, with 0.70 or greater considered normal. The FVC ranged from 46% to 72% predicted based on height, the FEV_1 from 39% to 68% predicted, and the FEV_1/FVC ratio from 0.69 to 1.00. All 8 patients experienced marked dyspnea after exercise. It was concluded that growth of the existing lung provided adequate pulmonary exchange, but a reduction in vital capacity and exercise tolerance could be demonstrated.[10] Measurements of neonatal lung function have shown lung overinflation and air trapping.[23] Spirometric studies in adults and older children have shown decreased FVCs and FEV_1s with normal or increased residual volumes, but emphysema was usually not present.[21-25] In one of these studies,[25] the decreased PEFR did not change with aerosolized bronchodilators or intravenous aminophylline. These obstructive spirometry patterns and associated obstructive symptoms could be due to abnormal collapsibility, compression, or angulation of the tracheobronchial tree.[26] One group of authors[21] believed that cases of tracheal compression by the pulmonary artery are rare and cannot account for the almost universal occurrence of bronchitis and wheezing. As of 1998, 15 cases of tracheal stenosis associated with pulmonary agenesis had been reported. These patients had respiratory symptoms that included wheezing that was refractory to pharmacotherapy.[23] A MEDLINE search with asthma and lung agenesis

yielded only a single reference, in Japanese, with no abstract available.[27]

The differential diagnosis focuses on other causes of an opaque hemithorax. These include diaphragmatic hernia, fibrothorax, adenomatoid cystic malformation, pulmonary sequestrations, total pulmonary collapse, and massive pleural effusions.[28] In the pediatric population, especially in a symptomatic patient, a foreign body must also be kept in mind. Since many patients with unilateral pulmonary agenesis are asymptomatic unless the normal lung is compromised by infection, they often first present during an acute respiratory infection. Based on acute respiratory symptoms and their abnormal chest x-ray films, these patients are often treated as having persistent pulmonary infiltrates or atelectasis that fails to resolve with antibiotic treatment.[29] They are often treated with frequent antibiotics, and the diagnosis is even further delayed.

The prognosis for a patient with pulmonary agenesis is variable and dependent on the presenting symptoms and associated anomalies. Poor prognostic signs include recurrent infections or a chronic cough. Right-sided agenesis carries a worse prognosis than left-sided agenesis secondary to rotation of the mediastinum to the right, which induces a greater degree of obstruction of the rotated main carina with impairment in bronchial drainage and increased susceptibility to pulmonary infection.[30] Right-sided agenesis also carries a greater degree of associated anomalies, which is another poor prognostic indicator. Asymptomatic cases do not require treatment. Management in symptomatic cases is usually supportive with chest physiotherapy and liberal use of antibiotics to treat recurrent pulmonary infections.[31]

CONCLUSION

To the best of our knowledge, this is the first case report of asthma in a patient with unilateral pulmonary agenesis. However, the question remains, "Does she have asthma or merely an anatomic obstruction?" Current asthma diagnostic methods, both subjective and objective, are inadequate in patients with significant anatomic defects. Perhaps in the near future, safer, noninvasive diagnostic modalities will be more widely available, such as measurement of exhaled nitric oxide, to aid in the evaluation of this patient. CT virtual bronchoscopy may help define an anatomical obstruction. An exercise challenge could be considered as a surrogate test, because it is believed to be safer than histamine challenge. In the meantime, we will continue to treat her clinically and question the diagnosis of asthma.

REFERENCES

1. Bernstein IL, Storms WW, Joint Task Force on Practice Parameters for Allergy Diagnostic Testing. Practice parameters for allergy diagnostic testing. *Ann Allergy Asthma Immunol.* 1995; 75:543–625.
2. Li JT, Lockey RF, Bernstein IL, Portnoy JM, Nicklas RA. Allergen immunotherapy: a practice parameter. *Ann Allergy Asthma Immunol.* 2003;90(Suppl 1):1–40.
3. Hargreave FE, Dolovich J, Newhouse MT. The assessment and treatment of asthma: a conference report. *J Allergy Clin Immunol.* 1990;85:1098–1111.
4. American Thoracic Society. Guidelines for methacholine and exercise challenge testing – 1999. *Am J Respir Crit Care Med.* 2000;161:309–329.
5. National Asthma Education and Prevention Program. *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma.* Washington, DC: National Institutes of Health; 1997. Publication 97–4051.
6. Boushey HA, Correy DB, Fahy JV. Asthma. In: Murray JF, Nadel JA. *Textbook of Respiratory Medicine.* 3rd ed. Philadelphia, PA: WB Saunders; 2000:789, 1266.
7. Brereton RJ, Rickwood AK. Esophageal atresia with pulmonary agenesis. *J Pediatr Surg.* 1983;18:618–620.
8. Bentsianov BL, Goldstein NA, Guiste R, Har-El G. Unilateral pulmonary agenesis presenting as an airway lesion. *Arch Otolaryngol Head Neck Surg.* 2000;126:1386–1389.
9. Viora E, Sciarrone A, Bastonero S, Errante G, Campogrande M. Prenatal diagnosis of isolated unilateral pulmonary agenesis in the second trimester. *Ultrasound Obstet Gynecol.* 2002;19: 206–207.
10. Maltz DL, Nadas AS. Agenesis of the lung: presentation of eight new cases and review of the literature. *Pediatrics.* 1968; 2:175–188.
11. Cunningham ML, Mann N. Pulmonary agenesis: a predictor of ipsilateral malformations. *Am J Med Genet.* 1997;70:391–398.
12. Schneider P, Schwalbe E. Die Morphologie der Mibbildungen der Menschen und der Thiere. *Gustav Fischer Jena.* 1912;3: 817–822.
13. Boyden E. Developmental anomalies of the lung. *Am J Surg.* 1955;89:79.
14. Booth JB, Berry CL. Unilateral pulmonary agenesis. *Arch Dis Child.* 1967;42:361–374.
15. Kravitz RM. Congenital malformations of the lung. *Pediatr Clin North Am.* 1994;41:453–472.
16. Conway K, Gibson RL, Perkins J, et al. Pulmonary agenesis: expansion of the VCFS phenotype. *Am J Med Genet.* 2002;113: 89–92.
17. Say B, Carpenter NJ. Pulmonary agenesis: importance of detailed cytogenetic studies. *Am J Med Genet.* 1998;76:446.
18. Thangjam N, Desai N, Menon RK, et al. Unilateral pulmonary agenesis with skeletal abnormalities. *Indian Pediatr.* 1983;20: 775–779.
19. Osborne J, Masel J, McCredie J. A spectrum of skeletal anomalies associated with pulmonary agenesis: possible neural crest injuries. *Pediatr Radiol.* 1989;19:425–432.
20. Berkenstadt M, Lev D, Achiron R, Rosner M, Barkai G. Pulmonary agenesis, microphthalmia, and diaphragmatic defect (PMD): new syndrome or association? *Am J Med Genet.* 1999; 86:6–8.
21. Massumi R, Taleghani M, Ellis I. Cardiorespiratory studies in congenital absence of one lung. *J Thorac Cardiovasc Surg.* 1966;51:561–568.
22. Kitagawa H, Nakada K, Fujioka T, et al. Unilateral pulmonary agenesis with tracheoesophageal fistula: a case report. *J Pediatr Surg.* 1995;10:1523–1525.
23. Nowotny T, Ahrens BC, Bittigau K, et al. Right-sided pulmonary aplasia: longitudinal lung function studies in two cases and comparison to results from term healthy neonates. *Pediatr Pulmonol.* 1998;26:138–144.

24. Clark H, Scott RB, Johnson JB. Pulmonary agenesis: roentgenographic and postmortem findings in one patient, hemodynamic and angiocardiographic findings in another. *Pediatrics*. 1955; 15:761–767.
25. Warner AL, Palladino NM, Schwartz W, Schuster A. The relationship of agenesis of the lung to emphysema and cor pulmonale. *J Pediatr*. 1955;46:200–209.
26. Maier HC, Gould WJ. Agenesis of the lung with vascular compression of the tracheobronchial tree. *J Pediatr*. 1953;43: 38–42.
27. Yamazaki K, Yamamoto H, Satohisa E, et al. A case of pregnancy complicated with congenital left lung agenesis [in Japanese]. *Acta Obstet Gynaecol Jpn*. 1994;46:1263–1266.
28. Guven S, Koyuturk Y, Cerrah Celayir A, Karadeniz L, Celikoglu S. An unusual cause of respiratory distress: unilateral pulmonary agenesis. *Arch Dis Child Fetal Neonatal Ed*. 2001;84:F197.
29. Bhasin RP, Mehdiratta KS. Pulmonary agenesis. *Indian Pediatr*. 1969;6:343–345.
30. Campanella C, Odell JA. Unilateral pulmonary agenesis: a report of 4 cases. *S Afr Med J*. 1987;71:785–787.
31. Tan KK, Chin CN. Unilateral pulmonary agenesis: an unusual cause of respiratory distress in the newborn. *Singapore Med J*. 1996;37:668–669.

Requests for reprints should be addressed to:
Melinda M. Rathkopf, MD
759 MDOS/MMIA
2200 Bergquist Dr
Suite 1
Lackland AFB, TX 78253
E-mail: melinda.rathkopf@lackland.af.mil