Pulmonary Presentation of Esophageal Leiomyomatosis Associated with Alport Syndrome in Childhood

Amir Kugelman MD[1], Yoel Greif MD[2], Ruth Gershoni-Baruch MD[3], Drora Berkowitz MD[4], Lael Anthon Best MB BS MS[5], Ludmila Guralnik MD[6] and Lea Bentur MD[7]

[1]Department of Neonatology, Bnai-Zion Medical Center, Haifa, Israel, [2]Pulmonary Division, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel [3]Department of Human Genetics, [4]Pediatric Gastroenterology Unit, [5]Department of Thoracic Surgery, [6]Department of Radiology, and [7]Pediatric Pulmonary Unit, Rambam Medical Center, Haifa, Israel
Affiliated to Technion Faculty of Medicine, Haifa, Israel

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Leiomyoma is the most common benign tumor of the esophagus but is rare in the pediatric age group [1,2]. Alport syndrome has been associated with leiomyomatosis [3,4]. Alport syndrome does not usually involve the lungs. We describe two patients who were referred to our Pediatric Pulmonary Clinic because of pulmonary disease related to esophageal leiomyomatotosis that was associated with Alport syndrome.

Patient Descriptions

Patient 1

This female patient, presently 14.5 years of age, suffered from severe vomiting during her first year of life. Subsequent evaluation included upper gastrointestinal barium study, esophageal manometry and endoscopy, which led to a diagnosis of achalasia. She underwent a modified Heller's myotomy at 3.5 years of age. At the age of 4, she was found to have microscopic hematuria with normal renal functions and normal renal ultrasonography. She had a family history of hearing loss; her hearing tests and eye examination were normal. At age 10, her vomiting increased and she had swallowing difficulties and hematemesis. Endoscopy showed a very dilated esophagus with severe distal esophagitis with polyps. Biopsies revealed epithelial metaplasia and severe esophagitis. Manometry showed a very low pressure at the lower esophageal sphincter area with almost no motility of the esophagus. A 24 hour pH monitoring demonstrated severe gastroesophageal reflux. An upper gastroesophageal barium study was compatible with achalasia. She was diagnosed as having severe gastroesophageal reflux secondary to Heller procedure and was treated with omeprazole, cisapride, and a high calorie diet. Repeat endoscopy showed amelioration of the esophagitis. Because of the persisting microscopic hematuria a renal biopsy was performed, demonstrating "thin glomerular basement membrane disease" that may be consistent with Alport syndrome.

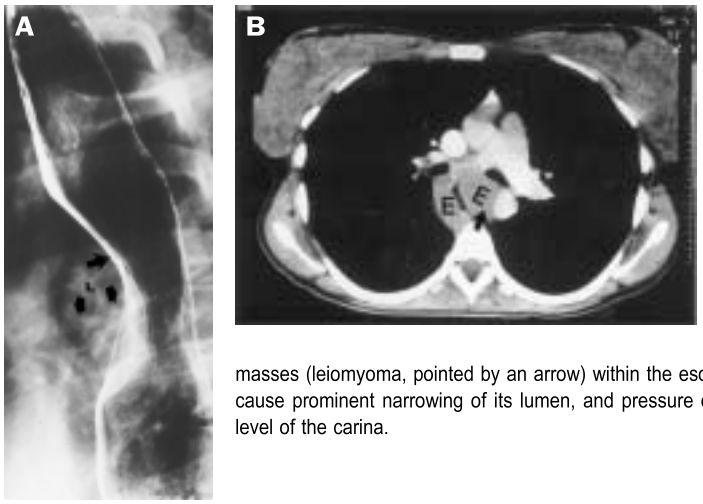
At the age of 11, the patient was referred to our Pediatric Pulmonary Clinic for evaluation of persistent cough, recurrent pneumonia and hyper-reactive airway disease with wheezing and exercise intolerance that responded to bronchodilators. Pulmonary function tests demonstrated moderate to severe reversible airway obstruction, with a forced expiratory volume at 1 sec of 58% and 73% of predicted value before and after bronchodilators, respectively. Computed tomography scan of the chest revealed normal lungs with no bronchiectasis, but there was diffuse thickening of the esophageal wall. Inhaled corticosteroids and long-acting beta-2 agonist were initiated. Six months later, the pulmonry function tests continued to show moderate to severe reversible airway obstruction (FEV1 of 47 and 80% of predicted value before and after bronchodilators). Repeat esophageal biopsy showed epithelial dysplasia and inflammation. Despite maximal pharmacotherapy, the patient continued to suffer from recurrent pneumonia and showed no improvement in her pulmonary function tests. At the age of 12 she underwent esophagectomy and gastric lifting, and her esophagus was found to have diffuse leiomyomatosis. After surgery, the pulmonary disease subsided, the cough disappeared and the pulmonary function tests showed marked improvement with FEV1 of 78% predicted value.

FEV1 = forced expiratory volume at 1 sec

Patient 2

A female patient presently 23 years of age was diagnosed at the age of 7.5 years by upper gastrointestinal X-ray study and endoscopy as having severe gastroesophageal reflux and esophagitis, with a thickened esophageal wall. A Nissen fundoplication was performed and she subsequently became asymptomatic. She was then found to have bilateral posterior cataracts. Hearing, urinalysis and renal function tests were normal.

During the last 6 years she complained of dyspnea and exercise intolerance, gradually worsening. More recently, she complained of dysphagia, vomiting and regurgitation, accompanied by a weight loss of 8 kg (she weighed 42 kg). The patient had noisy breathing with stridor and no clubbing. On physical examination, an enlarged clitoris was noted. Her evaluation included an esophageal and gastric endoscopy, an upper gastrointestinal X-ray study and a chest CT scan. These examinations demonstrated an esophageal mass that compressed the airway at the level of the carina [Figure]. Pulmonary function tests showed a fixed upper airway obstruction with air trapping (FEV1 of 14% of predicted value, residual volume of 299% of predicted value, residual volume/total lung capacity of 277% and flattening of the flow volume curve). Bronchoscopy revealed posterior



[A] Upper gastrointestinal barium study showing a mass (L-leiomyoma) that compress the anterior wall of the esophagus and the posterior wall of the trachea. The esophageal lumen is narrowed. **[B]** Chest CT scan showing masses (leiomyoma, pointed by an arrow) within the esophageal wall (E) that cause prominent narrowing of its lumen, and pressure on the airways at the level of the carina.

compression of the trachea and mucosal irregulation; biopsies were not performed. A total esophagectomy was performed with gastric lifting. Pathologic examination of the esophagus showed diffuse leiomyomatosis. A few months after surgery, the patient still had exercise intolerance, recurrent cough and a FEV1 that was 20–30% of predicted value.

Comment

Leiomyomatosis associated with Alport syndrome has been reported to be inherited as an X-linked dominant form due to deletions encompassing the 5′ ends of both COL4A5 and COL4A6 genes on chromosome Xq22 [3,4]. Alport syndrome is a hereditary disease that involves the kidneys and the eyes, and includes also sensorineural hearing loss. The spectrum of mutations is broad; penetrance may vary and this may explain the clinical heterogeneity of Alport syndrome and its associated features, such as esophageal leiomyomatosis and vulvar leiomyomatosis [3,4]. Both of our patients may well conform to the diagnosis of esophageal leiomyomatosis associated with Alport syndrome: the first patient because of renal involvement and familial hearing loss, and the second because of bilateral cataracts and enlargement of the clitoris.

Bourque et al. [1] reviewed 22 cases of esophageal leiomyoma in the pediatric population [1]. Contrary to the solitary and localized nature of the condition in adults, over 91% of the lesions in children were diffuse with multifocal discrete masses or even diffuse infiltrations of the esophageal wall; this latter entity is termed leiomyomatosis [2]. Twenty-two percent of diffuse leiomyomatosis is familial and associated with Alport syndrome [1,2]. Genital anomalies, such as hypertrophy or leiomyoma of the vulva or clitoris, occurred in half the cases [1]. Rarely, smooth muscle proliferation may involve the tracheobronchial tree [2]. Children with leiomyomatosis are more symptomatic than adults, probably due to the diffuse nature of their lesions and the relatively narrower esophagus and airways. The main complaints were dysphagia (86%), vomiting (27%), retrosternal pain (27%), weight loss and hematemesis; the symptoms often mimic achalasia. CT scan shows esophageal dilation with increased wall thickness, in contrast to a generally normal esophageal wall thickness in achalasia [1]. Considering the location, the size and the extent of leiomyomas in children, resection becomes the therapeutic procedure of choice. Seventy-eight percent of pediatric cases have needed partial or complete esophagectomy, with a 21% postoperative mortality rate [1].

The respiratory symptoms of esophageal leiomyoma in children are dyspnea in 36% and cough in 22% [1]. These respiratory manifestations, as well as the features of recurrent pneumonia, hyper-reactive airway disease and exercise intolerance, may mimic the respiratory symptoms of achalasia. In the second patient described, an upper airway obstruction was observed. This patient had stridor on physical examination and significant flattening of the flow-volume loop. Extensive leiomyomatosis may obstruct the trachea and bronchi by direct infiltration [2,3], or by the esophageal mass that can cause external compression of the upper airways. In this patient CT scan showed the external pressure on the trachea and major bronchi. While obstructive airway disease was reversible in the first patient, the second patient displayed minimal improvement and severe air trapping. The air trapping might be the result of persisting tracheobronchomalacia changes due to long-term extrinsic compression or to tracheal and airway involvement by diffuse leiomyomatosis. Air trapping could result from loss of elastic recoil of the lung because of ultrastructural changes in collagen and basement membrane shown in Alport syndrome [5].

In summary, we present two patients with diffuse leiomyomatosis associated with Alport syndrome with significant respiratory involvement.

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Correspondence: Dr. L. Bentur, Pediatric Pulmonology Unit, Rambam Medical Center, P.O. Box 9602, Haifa 31096, Israel.
Phone: (972-4) 854-2784
Fax: (972-4) 854-3127
email:dramir@netvision.net.il