Clinical-pathologic conference in general thoracic surgery: Malignant transformation of recurrent respiratory papillomatosis

Benjamin D. Kozower, MD
Cylen Javidan-Nejad, MD
James S. Lewis, MD
Shabbir Safdar, MD
Joel D. Cooper, MD
G. Alexander Patterson, MD

From the Washington University School of Medicine, Barnes-Jewish Hospital, St Louis, Mo. This case is available for further study on the World Wide Web at: www.mosby.com/jtcvs

Participants

From the Washington University School of Medicine, Barnes-Jewish Hospital, St Louis, Mo.

Thoracic Surgery

Dr Benjamin D. Kozower
Dr Joel D. Cooper
Dr G. Alexander Patterson

Radiology

Dr Cylen Javidan-Nejad

Surgical Pathology

Dr James S. Lewis

Medical Oncology

Dr Shabbir Safdar

Case Presentation

Dr Kozower: A 30-year-old woman presented with recurrent left-sided pneumonia and a left lower lobe lung abscess. She worked as a nurse but had been on disability for 6 months because of continuous purulent sputum production, fever, weight loss, and fatigue. Her past medical history is significant for recurrent respiratory papillomatosis, which has required numerous procedures to maintain a patent airway, including a tracheostomy performed in 1977. A previous left thoracotomy was performed at an outside hospital, but the procedure was abandoned because of technical difficulties with ventilation. She was referred here for evaluation and possible left lower lobe lobectomy.

She has no smoking history and does not consume any alcohol. She has 5 siblings, all of whom are in good health. She has no other significant past medical history. Her surgical history includes the tracheostomy performed at age 3 years and multiple bronchoscopies and airway interventions to maintain patency. On physical examination, she was very thin but appeared well. Her stoma was clean, with no signs of infection. She had no cervical or supraclavicular adenopathy, and her pulmonary examination was only significant for decreased breath sounds over the left base. The left thoracotomy incision was well healed. Bronchoscopic biopsy specimens from a large papilloma in her left lower lobe were performed at an outside hospital. The earliest was in April 2004 and showed some benign tracheal mucosa and papilloma. She had another biopsy 2 months later that showed some atypical cells in the left lower lobe bronchus.

Dr Javidan: The chest radiograph shows a tracheostomy tube, mediastinal widening suggestive of mediastinal lymphadenopathy, a left pleural effusion, and multiple nodules and masses in both lungs (Figure 1). Most of the masses are cavitated, and many have air fluid levels within them. These lesions are better evaluated with computed tomography (CT). CT shows multiple cavitating nodules and cystic lesions with varying degrees of wall thickening (Figure 2). These lesions are characteristic for adults with papillomatosis of the lungs.

In this patient the soft-tissue windows of the CT scan show a mass invading the left lower lobe bronchus, accompanied by distal segmental collapse of the postero-

From the Washington University School of Medicine, Barnes-Jewish Hospital, St Louis, Mo.

Received for publication June 3, 2005; accepted for publication June 16, 2005.

Address for reprints: Benjamin D. Kozower, MD, Washington University School of Medicine, Department of Cardiothoracic Surgery, Suite 3108 Queeny Tower, One Barnes-Jewish Hospital Plaza, St Louis, MO 63105 (E-mail: kozowerb@msnotes.wustl.edu).

J Thorac Cardiovasc Surg 2005;130:1190-3

0022-5223/\$30.00

Copyright © 2005 by The American Association for Thoracic Surgery

doi:10.1016/j.jtcvs.2005.06.036

Figure 1. Posteroanterior upright chest radiograph showing multiple cavitary masses containing fluid in the left lower lobe, a right suprahilar mass, a left pleural effusion, mediastinal widening, and left hilar enlargement, which is suggestive of lymphadenopathy.

basal segment of the left lower lobe and multiple cavitary lesions with irregular thick walls and mural nodules in the remainder of the left lower lobe (Figure 3). The soft-tissue mass and the cavitary lesions could represent papillomatosis or malignant transformation into squamous cell carcinoma.

In the left lower lobe there are some air- and fluid-filled dilated bronchi and bronchioles, which are due to postobstructive atelectasis in the setting of the slow-growing central mass growing into the left lower lobe bronchus. There are multiple enlarged lymph nodes in the mediastinum, many of which have centers of lower attenuation. This lymphadenopathy could represent superimposed infection, an abscess, human papilloma virus (HPV) infection, or metastatic lymphadenopathy resulting from malignant transformation.

There is a broad differential diagnosis for multiple, cavitating, thick-walled lesions. First is squamous cell cancer, primary or metastatic. HPV, Wegener's granulomatosis, and fungal infections are other causes. Because of this patient's history of respiratory papillomatosis and the risk for malignant transformation in the airways and lung parenchyma, I am most worried about squamous cell cancer. The lymphadenopathy is concerning but might be reactive to the HPV infection or lung abscess.

Figure 2. Computed tomographic lung window image shows a thinner-walled cystic lesion in the right lower lobe (short arrow) and a larger fluid-containing cavitary lesion in the left lower lobe with an irregular thick wall. Segmental collapse of the postero-basal segment of the left lower lobe is accompanied by more cavitary lesions.

Dr Patterson: Bear in mind that this patient had a tracheostomy performed when she was 3 years of age because of tracheal papillomatosis, and she has had hundreds, maybe thousands, of bronchoscopic debridements, laser, cautery, fulguration, etc. Her symptoms were chronic illness, continuous production of purulent sputum, constant coughing, and weight loss. All of her symptoms were attributed to that cavity in the lower lobe. In addition, she had a large papillomatous obstruction of her left lower lobe. About 6 months before coming here, she had a thoracotomy with the intent of removing that left lower lobe abscess or cavity. During the conduct of that operation, the patient had an episode of desaturation, and the surgeons abandoned the procedure, closing the thoracotomy. She was subsequently transferred here.

Dr Cooper: Was her larynx obstructed?

Dr Patterson: Yes, her upper airway was obliterated by a combination of scar and papillomatosis.

Dr Kozower: On December 6, we performed flexible and rigid bronchoscopy, which revealed extensive purulent secretions coming from both lungs. After these were suctioned, we determined the focus to be in her left lower lobe. In addition, there was a large papilloma seen in the left lower lobe, with a good cuff of proximal airway, and we thought that she would be a candidate for left lower lobe lobectomy. Given the enlarged lymph nodes that were seen

Figure 3. Computed tomographic soft-tissue window image shows a thick-walled cystic lesion with a mural nodule in the superior segment of the lower lobe. Medial and anterior to it, a soft-tissue mass extends into the left lower lobe bronchus, causing segmental collapse more distally (arrow).

on her CT scan, she underwent mediastinoscopy. Every lymph node station sampled was notable for large amounts of purulent material, but there was no evidence of malignancy at the frozen section. Subsequently, a very difficult left thoracotomy and left lower lobe lobectomy were performed.

Dr Lewis: Frozen section evaluation revealed squamous cell carcinoma on endobronchial biopsy of the mass but showed no evidence of malignancy in cervical, level 7 subcarinal, or level 4 lower paratracheal lymph nodes. We then received a 339-g, 11 × 10 × 8.5-cm left lower lobectomy specimen. This showed a 7.0-cm intraparenchymal, white-tan mass with a polypoid endobronchial component and areas of necrosis. Histologic examination showed dilated airways around the mass, with papillomatous surface lesions with well-developed fibrovascular cores. They were lined by bland, thickened squamous epithelium with little atypia or mitotic activity (Figure 4, A). Their surfaces blended into the surrounding flat respiratory-epithelium lined airway. They also blended into the exophytic surface component of a squamous cell carcinoma (Figure 4, B), where there was thicker epithelium and appreciable cytologic atypia and mitotic activity with individual degenerating cells. Beneath this, the majority of the mass consisted of moderately to well-differentiated squamous cell carcinoma with keratinization, necrosis, and surrounding stromal fibrosis (Figure 4, C and D). All lymph nodes analyzed were free of tumor, and the pleura was uninvolved. Surrounding airways had purulent material and dilatation, likely from obstruction and superinfection.

Figure 4. Microscopic pathology.

By means of pathologic analysis, the bland areas of papillomatosis were intimately associated with the dysplastic surface, as well as the invasive components of the squamous cell carcinoma, suggesting that the tumor originated from a papilloma.

Dr Cooper: What is the status of the bronchial margin? Alec, when you cut across the bronchus, were you cutting across this papillomatous obstruction? Finally, what was the status of the left upper lobe?

Dr Patterson: This was an extremely difficult resection. First we ligated the inferior pulmonary vein and the arterial branches to the left lower lobe. Then we dissected through this phlegmanous mass looking for the bronchus and found ourselves in it. We were a little downstream from the arteries, and therefore I knew we had good length. We were able to milk the tumor down into the airway and amputate the bronchus through tumor-free margins. The left upper lobe was relatively normal. There were fine nodular densities that we thought might be bronchiectasis or focal areas of papillomatosis.

Dr Lewis: Yes, the bronchial margin was free of tumor, and I think the nodular densities were probably papillomatosis, and the airway thickening is the result of chronic obstruction.

Dr Kozower: She had a fairly long postoperative course because of the infection in her pleural space. Her chest tubes were left in place for her 18-day postoperative stay, and she remained febrile for almost 2 weeks while receiving broad-spectrum antibiotics. Her basilar chest tube was eventually converted to an empyema tube, and she was afebrile and feeling much better at the time of discharge.

Recurrent respiratory papillomatosis typically presents with hoarseness and laryngeal obstruction in children. The disease tends to be more severe when presenting before the

age of 3 years, and most patients require removal of laryngeal papillomas every 2 to 3 months.¹ The vast majority of patients have papillomas confined to their larynx. Only 20% of cases involve the distal airways, and it is rare to involve the lung parenchyma.²

The incidence is 4 per 100,000 persons on the basis of US and Danish studies.³ This amounts to 2000 new cases per year in the United States. In children, 25% of the cases present during infancy, and the disease tends to be more severe and diffuse. In adults, 60% of the cases present during the ages of 20 to 30 years. Papillomas tend to be more focal, typically occurring in the trachea. The ability for papillomas to transform into squamous cell carcinoma is well described.^{4,5} However, it is quite rare for malignant transformation to occur in lungs without prior radiation. A few cases of squamous cell carcinoma arising in the lung parenchyma have been reported, and all of these patients have had HPV serotype 11. The cause is thought to be vertical transmission because 70% of the mothers are HPV positive. Although there are 90 serotypes for the HPV, only 4 have been found to cause recurrent respiratory papillomatosis.

Dr Safdar: Cytokine therapy is supposed to work in these cases. Was this patient ever treated with interferon or interleukin?

Dr Patterson: She has been under continuous care in Louisiana, but I do not know her detailed medical treatment history.

Dr Kozower: There are numerous treatment strategies, including interferon α 2a, retinoic acid, photodynamic therapy, indol-3-carbinol/diindolylmethane, and cidofovir. There is enthusiasm for cidofovir, which has demonstrated activity against pediatric and adult HPV infections. It is usually administered locally, but there is some evidence for system-

ically administered cidofovir for patients with recurrent respiratory papillomatosis with pulmonary involvement.⁶

Dr Lewis: We have seen at least 4 of these cases here. I think the patients with lung involvement end up with pulmonary destruction caused by airway obstruction and repeated pneumonias. More commonly, patients have an inability to control the growth of their tracheal papillomas, and they experience repeated airway obstruction.

Dr Safdar: I think we should treat her papillomatosis. Given her age and the fact that she has other areas of lung involvement, I think somebody should see her and decide on further treatment.

Dr Patterson: That is very reasonable. However, she was chronically ill and septic from her lung abscess, and it will be some time before she is ready for any additional therapy. She lives in Louisiana and has returned home this week. She is in contact with her referring pulmonary physician and a medical oncologist regarding subsequent treatment.

References

1. Doyle DJ, Henderson LA, LeJeune FE Jr, et al. Recurrent respiratory papillomatosis: juvenile vs. adult forms. *Laryngoscope*. 1994;104:523-7.
2. Ray R, Debich-Spicer D, Forrego O, et al. Pathological case of the month. *Arch Pediatr Adolesc Med*. 1998;152:407-8.
3. Lindeberg H, Elbrond O. Laryngeal papillomas: the epidemiology in a Danish subpopulation 1965-1984. *Clin Otolaryngol*. 1990;15:125-31.
4. Solomon D, Smith RR, Kashima HK, et al. Malignant transformation in non-irradiated recurrent respiratory papillomatosis. *Laryngoscope*. 1985;95:900-4.
5. Lele SM, Pou AM, Ventura K, et al. Molecular events in the progression of recurrent respiratory papillomatosis to carcinoma. *Arch Pathol Lab Med*. 2002;126:1184-8.
6. Armbruster C, Kreuzer A, Vorbach H, et al. Successful treatment of severe respiratory papillomatosis with intravenous cidofovir and interferon α -2b. *Eur Respir J*. 2001;17:830-1.