Clinical-pathologic conference in general thoracic surgery: Carinal resection for endobronchial grade I neuroendocrine carcinoma

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Case Presentation

Dr Kozower: A 20-year-old woman presented with a 2-month history of expiratory wheeze and dry cough. Her symptoms gradually worsened, and exertional dyspnea developed. She denied weight loss, fever, hemoptysis, or neurologic symptoms. Her internist prescribed bronchodilators for reactive airway disease, but her condition did not improve. A chest radiograph was abnormal, and she was referred to a thoracic surgeon.

She was in excellent health, with no significant past medical history. She took no medication and never had an operation. She is a lifetime nonsmoker and does not consume alcohol. On physical examination, she was a healthy appearing 20-year-old woman. She was afebrile and had no cervical or supraclavicular adenopathy. The results of her cardiac examination were normal. She had absent breath sounds on the right, with diminished chest wall excursion. Her extremity examination revealed no clubbing, cyanosis, or edema.

Dr Bhalla: Her initial chest radiograph is a dramatic demonstration of a mass extending into the right main-stem bronchus and distal trachea (Figure 1). The left main-stem bronchus appears uninvolved. There is complete collapse of the right lung, with herniation of the heart toward the right. A computed tomographic (CT) scan was obtained that shows an enhancing mass in the distal trachea and right main-stem bronchus (Figure 2). There are a few lymph nodes present around the airway, and there is another lymph node anterior to the mass in the region of the right hilum. The right lung is collapsed, and the mediastinum is shifted toward the right. In addition, there is a small pericardial effusion, pleural effusion, and some dilated bronchi.

The CT appearance is highly suggestive of a neuroendocrine tumor in this young woman. There is a mass associated with the bronchus that enhances with intravenous contrast and is associated with volume loss. The other thing that can occasionally have this appearance is an inflammatory myofibroblastic pseudotumor. However, those tend not to enhance with intravenous contrast. To complete the differential diagnosis, certain metastases, such as melanoma, can have a similar appearance on CT, but she has no history of a prior malignancy. In conclusion, the CT findings are most suggestive of a neuroendocrine tumor. The enlarged lymph nodes seen on CT scanning are not very useful in predicting tumor grade.

Dr Miller: This is a classic nuclear medicine study for right bronchial obstruction. The right lung has no ventilation, and the left lung is ventilated normally. In the perfusion scan the left lung is normal, and the right lung has very diminished perfusion. The differential diagnosis for this is a central obstructing mass, foreign body aspiration, mucous plug, or fibrosing mediastinitis.

Dr Kozower: She was taken to the operating room for fiberoptic and rigid bronchoscopy. The mass completely occluded the right main-stem bronchus and was adherent to the posterior wall of the carina (Figure 3). The left main-stem bronchus was patent.

Figure 1. Chest radiograph. Anteroposterior chest radiograph shows complete opacification of the right hemithorax and volume loss. The left lung herniates over to the right. A large polypoid mass arises from the right main-stem bronchus.

Dr Patterson: You really could not see her tracheal carina. Our goal was to obtain a tissue diagnosis and core out the lesion. I thought that we would be able to open up the right main-stem bronchus enough to facilitate re-expansion of that

Figure 2. Chest computed tomographic scan. Noncontiguous axial images from a contrast-enhanced computed tomographic scan show complete volume loss from the central mass (black arrow). The mass enhances compared with skeletal muscle. Enhancing hilar lymphadenopathy (arrowhead) and dilated bronchi (white arrows) were also noted. The constellation of an enhancing, central, airway-related mass with dilated bronchi and lung collapse is characteristic of carcinoid tumors.

lung, followed by a parenchymal sparing resection of the presumed carcinoid. However, the lesion was very difficult to core out, and we never achieved satisfactory ventilation of the right lung.

Dr Kozower: We took a biopsy specimen of the mass, and the frozen section diagnosis was consistent with a grade I neuroendocrine tumor or typical carcinoid. We then cored out the tumor with a rigid bronchoscope. It was difficult to establish a patent airway in the right bronchus, but there was some aeration of the right lung after the procedure. We decided to wait 2 weeks before resection to see whether the right lung ventilation would improve and to give her a chance to clear some of her secretions.

Our surgical plan was to perform a carinal resection with right upper lobe sleeve resection. The procedure began with a cervical mediastinoscopy to stage the mediastinal lymph nodes and help dissect the distal trachea and right main-stem bronchus. A right posterolateral thoracotomy was then performed. The obstructing mass extended from the posterior wall of the distal trachea to the distal bronchus intermedius. It appeared to originate from the right main-stem bronchus, and there was no way to preserve the right upper lobe. The bronchus intermedius was divided first, followed by the left main-stem bronchus and trachea. We resected the right upper lobe en bloc with the airway margins and used cross-field ventilation to facilitate the procedure. We then performed a radical mediastinal lymphadenectomy to remove any macroscopic disease. Negative airway margins

Figure 3. Initial bronchoscopy. Fiberoptic bronchoscopy revealed a mass that completely occluded the right main-stem bronchus and was adherent to the posterior wall of the carina. The left main-stem bronchus was patent.

Figure 4. Postresection bronchoscopy. Fiberoptic bronchoscopy 3 months postoperatively revealed a patent and viable neocarina. Most of the bronchus intermedius has been resected, and the right middle and lower lobe bronchi are visible.

were confirmed with frozen section analysis before starting the anastomoses.

We performed a right hilar release to elevate the bronchus intermedius and decrease tension on the airway anastomoses. The reconstruction was begun by sewing the left main-stem bronchus to the bronchus intermedius to create a new carina. The neocarina was then sutured to the distal trachea. Her postoperative course went quite smoothly, and she was discharged to home in 6 days. She is doing well 3 months postoperatively, and her bronchoscopy reveals a patent and viable airway with minimal granulation tissue (Figure 4).

Dr Jarrett: A low-power (4×) image of a biopsy specimen of the patient's intratracheal tumor shows the tumor cells arranged in small nests (Figure 5, A). A higher-power picture (60×) shows the "salt-and-pepper" chromatin pattern classically associated with carcinoid tumor (Figure 5, B). No necrosis or mitoses are evident.

Histology of the resected specimen shows an intrabronchial tumor with extension across the airway cartilage into the lung parenchyma. The nested architecture is identical to that seen in the biopsy specimen. As in the biopsy specimen, necrosis and mitoses are not seen (Figure 5, C). A higher-power image shows that the cells are bland and relatively monotonous appearing, with the classic salt-and-pepper

Figure 5. A, Low-power image (4×) of the biopsy specimen shows the tumor cells arranged in small nests. B, High-power image (60×) of the biopsy specimen shows the salt-and-pepper chromatin pattern classically associated with carcinoid tumor. No necrosis or mitoses are evident. C, Low-power image (2×) of the resected specimen shows intrabronchial tumor with extension across the airway cartilage into the lung parenchyma. The nasal architecture is identical to that seen in the biopsy specimen. D, Higher-power image (40×) shows that the cells are bland and relatively monotonous appearing, with the classic salt-and-pepper chromatin pattern of grade I neuroendocrine tumors.

chromatin pattern (Figure 5, D). Frozen section of the left main bronchial margin showed no evidence of tumor. However, deeper levels cut for routine permanent sections showed carcinoid tumor.

Thirty-one lymph nodes were sent for examination, and 6 showed metastatic carcinoid tumor at levels 4R (right paratracheal) and 7 (subcarinal). Several of the positive lymph nodes had been received for frozen section analysis. Because cytologic features of carcinoid tumor are not well represented on tissue that has been frozen, confirmatory immunohistochemistry was performed on those nodes. The synaptophysin stain was strongly positive and highlights the role of neuroendocrine markers in the diagnosis of carcinoid tumor.

The spectrum of neuroendocrine tumors was classified by Dressler and associates¹ on the basis of histologic characteristics and clinical behavior. Grade I neuroendocrine lung cancers correspond to classic typical carcinoid tumors. Grade II neuroendocrine lung cancers correspond most closely with atypical carcinoid cancers. Grade III tumors were divided into small cell neuroendocrine lung cancer and large cell neuroendocrine lung cancers.

Grade I neuroendocrine tumors are commonly divided into central and peripheral varieties. They are characterized histologically by the lack of cytologic atypia, low mitotic rate, and absent necrosis. Grade I neuroendocrine lung

cancers can be arranged in nested architecture, ribbons, festoons, trabeculae, or papillae; show solid sheet-like growth; or both. Because central carcinoids usually have a significant intraluminal component, patients often present with wheezing, obstruction, and pneumonia. Overall, cases of typical carcinoids have an excellent prognosis. Unfavorable prognostic features include size greater than 3 cm, vessel invasion, and lymph node invasion. Lymph node metastases are rare in typical carcinoids.²

Dr Kozower: This is a classic presentation for a young woman with a carcinoid tumor. Unfortunately, she has extensive N2 disease, and there are relatively little data to predict her prognosis or help guide her treatment. Martini and associates³ published a small series on the treatment and prognosis of bronchial carcinoids involving regional lymph nodes. It was a small retrospective review of 25 patients treated between 1953 and 1992. Ten patients had N1 disease, and 15 patients had N2 disease. There were 13 atypical and 12 typical carcinoids. The 5-year actuarial survival for the whole group was relatively high at 75%. Importantly, the 5-year survival was 92% for the 12 patients with typical carcinoids, despite having positive lymph nodes. In addition, there was no difference in survival between patients with N1 disease and those with N2 disease. The authors concluded that the grade of neuroendocrine carcinoma is a more important predictor of survival than the presence of lymph node metastases. In addition, the use of adjuvant radiation therapy for N2 disease did not appear beneficial.

Our patient is 20 years old and has a grade I neuroendocrine carcinoma. However, the final pathology indicates that she has multiple-station N2 disease and a positive airway margin. How comfortable should surgeons be with frozen section analysis of the margins, and does she need any additional treatment at this time?

Dr Ritter: The margins on the frozen section slides were negative, and it is difficult to interpret the final diagnosis. If you have a truly negative margin and we cut deeper into that section to find tumor, I would argue that the margin is in fact still negative. The reality is that the margin is very close, but I am not so sure that I would consider it to be positive.

Dr Patterson: The margins in this case are extremely important, and I also think we have a negative margin. In a case like this, where the margins will alter our treatment decisions, we excise a section and orient it with a suture at the true margin. The margin in question in this case is the proximal left main bronchus. The pathologists, as Dr Ritter

pointed out, sectioned the distal edge of that airway intraoperatively, and it was negative. However, when they cut deeper into the specimen, further from our margin, there was tumor. I realize that the margin was very close, but it is a difficult place to excise more bronchus when you are trying to perform a carinal sleeve resection.

The reality is that even if the margin is positive, I would not do anything about it. Technically, we cannot re-resect her. Radiation will not help because these tumors do not respond well to radiation and you would expose a carinal anastomosis to the risks of radiation therapy. I would argue that because the bronchial margin is close and because of her positive lymph nodes, she should have surveillance bronchoscopies and chest CT scans done at regular intervals. If she has a local recurrence at the anastomosis, I would be inclined to treat her endoscopically. If she had a recurrence years from now, one could argue that some sort of local resection could be attempted. I think that the bigger problem for her is her nodal metastases. She is 20 years old and has multistation N2 disease.

Dr Kozower: After reviewing the literature, it is difficult to determine how to treat her, and adjuvant therapy does not appear to be very helpful. How many patients have been treated with grade I neuroendocrine carcinoma and bulky N2 nodes? Dr Safdar, do you have any comments on the use of adjuvant therapy in this case?

Dr Safdar: I agree that we do not have good adjuvant therapy for low-grade neuroendocrine carcinomas. We have occasionally radiated some of these patients, but as Dr Patterson stated, she is not a good radiation therapy candidate.

This is an excellent example of a case that demonstrates that the histology of certain tumors can only tell you so much. There is not a single clue from the primary tumor that would predict that it is likely to metastasize. It is large, but there is no necrosis, and the mitotic rate is negligible. It illustrates that our understanding of neuroendocrine carcinomas remains imprecise.

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