Clinical-pathologic conference in general thoracic surgery: A malignant peripheral nerve sheath tumor of the trachea

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Case Presentation

Dr Shah: A 63-year-old man with a 5-pack-year smoking history presented to our institution for management of progressive dyspnea. He was diagnosed with bronchial asthma yet had not responded to inhaled β -agonists or oral steroids. His past surgical history was significant for cervical laminectomy 9 years ago and left eye vitrectomy 1 year ago. His medical history was significant for adult-onset diabetes mellitus, hypertension, and hyperlipidemia. He also had remote exposure to tuberculosis and 2 episodes of pneumonia over the past 24 months. Physical examination revealed expiratory, as well as inspiratory, stridor throughout both lung fields without rales or ronchi. Baseline laboratory tests were significant for a blood glucose level of 210 mg/dL, a blood urea nitrogen level of 50 mg/dL, and a creatinine level of 2.4 mg/dL. Forced expiratory volume in 1 second, forced vital capacity, forced expiratory volume in 1 second/forced vital capacity, and diffusion capacity, were 20%, 86%, 70.3%, and 84% of predicted values, respectively. Resting oxygen saturation was normal. Configuration of the flow-volume loop was suggestive of variable intrathoracic upper airway obstruction, with reduction in peak expiratory flow to 22% of predicted value.

Dr Karnak: Dr Shah, could you please describe the radiographic and chest computed tomographic (CT) findings?

Dr Shah: The chest radiograph showed a 2×2.5 -cm opacity projected over the distal trachea on the frontal view; the lateral view was unremarkable. The noncontrast axial CT image at the level just above the carina ([Figure 1](#)) and the reconstructed midline sagittal and coronal image ([Figure 2](#)) in soft tissue windows demonstrated a lobulated transmural solid mass involving the distal anterior tracheal wall 1.5 cm proximal to the carina. The $3.2 \times 2.2 \times 3.2$ -cm extraluminal pretracheal component was coarsely calcified, whereas the $2.2 \times 2.3 \times 1.6$ -cm endobronchial components predominantly exhibited soft tissue density, with only a thin rim of calcification at its interface with the distal anterior tracheal wall. There was near-total occlusion of the distal trachea. The differential diagnosis included primary tracheal neoplasm (eg, squamous cell carcinoma, adenoid cystic carcinoma, bronchial adenoma, and carcinoid tumor) or metastasis (breast cancer, renal cell carcinoma, colon carcinoma, or melanoma). Tracheal chondroma and paratracheal nerve sheath tumor were believed to be less likely possibilities, given their lower incidence.

Dr Shah: Drs Mehta and Karnak, could you describe the bronchoscopic examination and intervention?

Dr Karnak: Flexible bronchoscopy revealed a lobulated, smooth, exophytic mass located approximately 2 cm above the carina and producing 80% obstruction of the tracheal lumen. When the bronchoscope was negotiated beyond the obstruction, there was no evidence of distal disease.

Dr Mehta: By using an electrocautery snare through the flexible bronchoscope after achievement of general anesthesia, the endobronchial portion of the tumor was resected ([Figure 3](#)).

Figure 1. A lobulated transmurial solid mass was seen 1.5 cm proximal to the carina. The *long arrow* shows a $3.2 \times 2.2 \times 3.2$ -cm pretracheal component, which is coarsely calcified. The *short arrow* shows a $2.2 \times 2.3 \times 1.6$ -cm exophytic soft tissue density with a thin rim of calcification.

Dr Shah: Dr Biscotti, could you describe the histopathology of the lesion?

Dr Biscotti: The tumor appeared similar in the endobronchial resection and the distal tracheal resection. The tumor involved the full thickness of the tracheal wall. The tumor had a highly cellular spindle cell component immediately underlying the epithelium (Figure 4). Elsewhere, tumor cells had a more epithelioid appearance and more nuclear atypical and mitotic activity (Figure 5). Peripheral zones had abundant collagen and less cellularity. Foci of mature metaplastic bone were identified, including an incomplete peripheral rim. The morphologic differential diagnosis included myofibroblastic, myoepithelial, melanocytic, epithelial, and peripheral nerve sheath tumors (MPNSTs). The tumor cells did not stain for the epithelial markers AE1/AE3 or CAM 5.2. The myoid/myofibroblastic markers smooth muscle actin, desmin, and caldesmon were negative. CD34 immunostain, a sensitive marker for solitary fibrosis

Figure 3. Exophytic tumor involving the lower part of the trachea.

tumor and its malignant variants, was also negative. The myoepithelial marker p-63 was also negative. The tumor had distinct areas of strong S100 positivity but lacked staining for more specific melanocytic markers, including HMB45, melan-A, and tyrosinase. Thus, taken in aggregate, the morphologic and immunohistochemical features favored an unusual low-grade malignant variant of MPNST.

Dr Shah: Dr Murthy, at this time, what should be the further plan of action?

Dr Murthy: I suggest surgical staging of the tumor before resection, with subsequent resection of the remainder of the tumor and reconstruction of the distal trachea and the carina.

Dr Shah: Dr Murthy, for our surgical colleagues, would you describe the details of the tracheal resection and reconstruction techniques.

Dr Murthy: After review of the CT scan and extensive discussions between members of the medical oncology,

Figure 2. Coronal oblique image shows obstruction caused by the endophytic mass.

Figure 4. The tumor periphery underlying the tracheal mucosa has a cellular spindle cell appearance.

Figure 5. This field illustrates a more epithelioid appearance. Mitosis is present (center).

radiation oncology, interventional pulmonology, and general thoracic surgery services, it was believed that surgical exploration with intended resection was the most appropriate option.

In the surgical suite, after induction of anesthesia, an extended right posterolateral thoracotomy with division of a latissimus muscle and mobilization of the serratus muscle was performed. Interspace 4 was entered. Initially, a single lumen tube was used to control the airway, with a bronchial blocker used to provide right-lung collapse. The densely calcified mass was easily appreciated in the middle mediastinum and distal trachea. There was significant deformity of the superior vena cava (SVC) caused by displacement by the extraluminal component of the mass. The SVC was circumferentially dissected above and below the mass, and vessel loops were used to control it. The azygous vein was divided as it coursed over the lateral aspect of the tumor, and a plane developed between the SVC and the mediastinal component of the tumor. Although dense adhesions existed between the 2 structures, there was no frank involvement of the vein that required en bloc venous resection. After the SVC was completely mobilized from the mass, the distal trachea was dissected circumferentially, with great care being taken to avoid injury to the left recurrent nerve. The trachea was controlled proximal and distal to the mass. The mass appeared to extend to the level of the carina, and dissection on the anterior aspect of the left main stem underneath the main pulmonary artery was performed bluntly. In addition, the membranous portion of the left main stem and trachea were dissected off the esophagus and mobilized completely. Circumferential dissection of the left main stem or proximal trachea was not undertaken for fear of devascularizing these structures. A right-sided hilar release maneuver was performed as the pericardium was circumferentially incised around the pulmonary veins. Great care was taken to avoid direct injury or traction on the phrenic nerve anteriorly, and the pericardiotomy was con-

tinued posteriorly to allow for full mobilization of the pulmonary veins. With the airway sufficiently mobilized proximally and distally, ventilation was held, and the trachea was divided sharply above and below the mass. The length of the resected trachea was approximately 3 cm. The distal resection margin was at the level of the carina approximately 2 to 3 mm from the septum separating the left and right main stem. Once the trachea was opened, an endotracheal tube was placed cross-table through the operative field into the left main stem, and single left-lung ventilation was resumed. The specimen was sent for frozen margins, and during that period of time, additional tracheal mobilization was performed. The left main stem was also further mobilized anteriorly and posteriorly, and after the right-sided hilar release maneuver, the proximal and distal cut ends appeared to coapt without excessive tension.

Because pathologic examination of the specimen revealed negative tracheal margins, the airway was reconstructed with a posterior continuous 4-0 Prolene suture (Ethicon, Inc, Somerville, NJ) to approximate the membranous airway and an anterior row of interrupted 4-0 Prolene sutures to oppose the cartilaginous airway. Intermittent apnea was used to complete the anastomosis, with the cross-table endotracheal tube being inserted as needed when the patient began to desaturate. After all sutures were placed, a jet-ventilating catheter was passed through the original oral endotracheal tube and guided into the left main stem. This allowed for ipsilateral lung collapse during the remaining portion of the procedure. When the anastomosis was secured, a pedicled flap of pericardium with attached fat pad was mobilized anteriorly and interposed between the SVC and the reconstructed airway. The jet catheter was then removed, and bilateral ventilation resumed through the original endotracheal tube. The anastomosis was leak tested and found to be pneumostatic to 25 cm of applied water pressure, and intraoperative bronchoscopy demonstrated airway patency. After chest closure and repositioning, the patient was successfully extubated in the operating theater. After a 1-day intensive care unit stay, the patient had an uneventful hospital course and was discharged home on postoperative day 5. Surveillance bronchoscopy at 8 weeks demonstrated a well-healed anastomosis, and the patient returned to work shortly after this visit.

Dr Shah: After surgical resection of the distal trachea with reconstruction, the tissue was sent for pathologic analysis (Figure 6). Dr Biscotti, could you describe the pathologic findings of the excised distal trachea?

Dr Biscotti: In this specimen the neoplasm has malignant features, including an infiltrative pattern with vascular invasion (Figure 7). The immunostaining and histopathologic findings were the same as I described before. The tracheal resection margins were negative for neoplasm. The distal tracheal specimen was also consistent with low-grade

Figure 6. Reconstructed distal trachea.

malignant epithelioid and spindle cell neoplasm, most consistent with a peripheral nerve sheath sarcoma.

Dr Shah: Primary tracheal neoplasms are rare, representing only 0.2% of all respiratory tract malignancies.¹ Sarcomas are even less common, representing less than 0.1% of all tracheal tumors.²

This low-grade malignant tracheal neoplasm has morphologic and immunohistochemical features most consistent with an unusual variant of a low-grade MPNST. Malignant peripheral nerve sheath tumors are rare, with an incidence in the general population of 0.001%. Approximately half of the patients with these tumors are genetically predisposed with neurofibromatosis 1 (NF-1), in which the incidence has been reported to be as high as 29%, where 5% to 13% of these tumors eventually become malignant after a long latent period of 10 to 20 years.³⁻⁵ However, more recent data have demonstrated the incidence of MPNSTs even in this predisposed population to be much lower (approximately 3%-5%), with malignant transformation being restricted to the larger plexiform neurofibromas.

The most common location is the lower extremities, but they can occur in other sites as well.^{6,7} They usually involve large nerves, such as the cervical and lumbar plexus. Grossly, the neoplasms present as large fusiform, spherical, or ovoid masses. Tumor spread is common, largely hematogenous, and most frequently to lung and bones. Lymph node metastases are rare.¹ Tumor necrosis and calcifications are common, often making subtype differentiation difficult.⁸ The tumor in our patient probably originated from tracheal nerve sheaths and invaded the lymph node nearby. Because other mediastinal structures were normal, we do not think it originated from the mediastinal nerves that invaded the trachea and the related lymph node. Moreover, the extratra-

Figure 7. The tumor invades a vascular space at the periphery.

cheal portion of the tumor that was calcified in our patient has also been described previously.⁹ We believe that this calcification was primarily related to the MPNST because there was no evidence of calcification involving any other lymph nodes. Factors that affect the prognosis in MPNSTs seem to be the size of the neoplasm and its association with NF-1.⁹ Neoplasms less than 10 cm in diameter have better prognosis than larger ones. If removed completely before it metastasizes, the prognosis is good. The 5-year survival is 15% in patients with NF-1 and 50% in patients without NF-1. After the surgical excision, we expect our patient's survival to be excellent.

Dr Shah: Radiologic appearance is often nonspecific yet characteristic. CT scans and magnetic resonance imaging (MRI) show a fusiform or dumbbell-shaped mass along the course of the nerve, a finding common to all neurogenic tumors. MPNSTs usually involve major nerve trunks, including the sciatic nerve and the brachial and sacral plexuses. Typically, on CT scan they are hypodense and show little enhancement after intravenous contrast. On MRI, they are of intermediate signal on T1-weighted sequences and relatively high signal on T2-weighted sequences, with enhancement seen in two thirds of the cases.^{9,10} MRI is believed to be superior to CT in characterizing MPNSTs, given its inherent soft tissue contrast, larger field of view, and multiplanar capabilities. Although features such as size less than 5 cm and well-defined margins are indicative of benignity, the tumor in our case is suspicious for malignant transformation based on its heterogeneity and invasion of soft tissue plane (ie, the tracheal wall).^{9,10}

Dr Shah: Radical surgical intervention involving extensive local excision appears to be the mainstay of treatment. Frozen sections of the proximal ends of nerves should be examined to ensure complete excision.^{11,12} The benefit of adjuvant radiotherapy in the treatment of MPNST has been questionable, whereas the benefit of adjuvant chemotherapy remains inconclusive. Some success has been reported with doxorubicin alone or in combination with other drugs.¹³⁻¹⁹

The patient was presented to the sarcoma tumor board and lung tumor board, and with the consensus of both groups, adjuvant radiotherapy was planned to reduce the risk of local recurrence. Follow-up CT scanning revealed no recurrence or lymphadenopathy. The trachea received a dose of 50 Gy with a boost field of 10 Gy; total dose to the tumor bed was 60 Gy. The patient tolerated the procedure well and will return in 6 weeks.

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