CASE REPORT

Bronchial-oesophageal fistula: a rare initial presentation of squamous cell carcinoma of the lung

Narjust Duma,¹ Christian Barlow,² Larysa Sanchez,³ Sean Sadikot⁴

¹Department of Internal Medicine, Rutgers-NJMS, Newark, New Jersey, USA

²Saint Georges University, True Blue, Grenada

³Rutgers-NJMS, Newark, New Jersey, USA

⁴Hackensack University Medical Center, Hackensack, New Jersey, USA

Correspondence to

Dr Narjust Duma, narjustperezmd@gmail.com

Accepted 22 May 2015

SUMMARY

A 61-year-old Caucasian man with hypertension and hepatitis C presented to the emergency department with 7 days of productive cough and low-grade fevers despite outpatient therapy with oral azithromycin. On initial evaluation, he was lethargic with peripheral cyanosis and oxygen saturation in the low 70 s on room air, necessitating endotracheal intubation. Chest imaging revealed diffuse bilateral infiltrates compatible with the diagnosis of acute respiratory distress syndrome. Patient subsequently developed profound hypoxaemia and on day 2 of admission, veno-veno extracorporeal membrane oxygenation (ECMO) was initiated. Bronchoscopy revealed a necrotic ulcer on the posterior wall of the left mainstem bronchus, compatible with a bronchial-oesophageal fistula, which was later confirmed by endoscopy, and stented. Histology revealed poorly differentiated squamous cell carcinoma of the lung. Despite stenting of the fistula and ECMO support, the patient expired 5 days after admission.

pack-year smoking history and heavy alcohol use, with the patient having quit both habits 5 years prior to presentation. Family history was negative for early cardiovascular disease or cancer.

On initial evaluation, the patient was lethargic and in acute respiratory distress. Peripheral cyanosis was noted, accompanied of a heart rate of 120 bpm and oxygen saturation in the low 70 s on room air. Lung auscultation revealed diffuse rhonchi in both lung fields and decreased breath sounds over the right lower lobe. The patient's complete blood count revealed leucocytosis of 11.1 μ L with 75% neutrophils, anaemia (haemoglobin 8.9 g/dL) with elevated mean corpuscular volume (102.6 fL) and thrombocytopenia (87 000/mm³). His chemistry was notable for acidosis with an anion gap of 31 mEq/L. Arterial blood gas revealed hypoxia with a PH of 7.01, PO₂ of 63 mm Hg and CO₂ 51 mm Hg. Non-invasive ventilation was initiated; however, the patient's respiratory status worsened, necessitating endotracheal intubation.

BACKGROUND

The clinical presentation of pulmonary malignancy may assume a number of diverse and multifaceted appearances. Among these, malignant tracheo-oesophageal fistula (TOF) remains one of the more serious possibilities. This may result from direct tumour extension into the mediastinum or from trachea-oesophageal injury due to instrumentation or local treatment. TOF formation in the setting of cancer is often fatal, and remains a potential and difficult obstacle in patient management. Oesophageal carcinoma is more frequently responsible than pulmonary malignancy,¹ in which TOF is found in <1% of the patient population.² TOFs are more frequently seen following chemoradiation with or without concomitant antiangiogenic agents.^{3 4} Our patient experienced a rare instance of TOF as the presenting feature of a newly diagnosed squamous cell carcinoma of the lung, with subsequent acute respiratory distress syndrome (ARDS) and multiorgan failure.

CASE PRESENTATION

A 61-year-old Caucasian man with a medical history of hypertension, alcohol abuse and liver cirrhosis secondary to hepatitis C, presented to the emergency department with 7 days of productive cough and low-grade fevers despite outpatient therapy with oral azithromycin. On interrogation, the patient's wife reported of him having an unintentional weight loss of five pounds in the past 2 months. Social history was significant for a 20

INVESTIGATIONS

Imaging studies conducted included: chest X-rays, CT, bedside bronchoscopy and upper endoscopy. On admission, portable chest X-rays showed extensive alveolar infiltrate throughout the right lung field with progressive and diffuse pleural parenchymal opacification (figure 1). Later CT of the chest demonstrated mild right pleural effusion and a moderate left pleural effusion. Extensive bilateral consolidation was seen throughout both lung fields as well as reticulonodular and ground-glass infiltrates, predominantly in the upper lung fields (figure 2).

Figure 1 Admission portable chest X-rays showed extensive alveolar infiltrate throughout the right lung field and progressive and diffuse pleural parenchymal opacification.

CrossMark

To cite: Duma N, Barlow C, Sanchez L, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-209103

Figure 2 Extensive bilateral consolidation seen throughout both lungs as well as reticulonodular and ground-glass infiltrate, predominantly within the upper lung fields. Mild right pleural effusion and a mild to moderate left pleural effusion.

Bronchoscopy was performed to collect additional culture specimens and to evaluate the upper respiratory tract, but instead revealed a necrotic ulcer on the posterior wall of the left mainstem bronchus compatible with a bronchial-oesophageal fistula (figures 3 and 4). Distally, the left airways were patent, although bronchitic changes were noted. Histological samples of the ulcer were taken. No endobronchial lesions were noted on the right mainstem bronchus. There were thin bilious secretions throughout the airways.

Bedside upper endoscopy failed to reveal any oesophageal varices or erosions, but did demonstrate a mid-level bronchial-oesophageal fistula. The stomach showed no signs of active bleeding, though erosive gastritis was observed with minimal bleeding on scope contact.

DIFFERENTIAL DIAGNOSIS

Morphology and immunohistochemistry of the ulcer/fistula revealed malignant cells, most likely reflective of a poorly differentiated squamous cell carcinoma of primary lung origin, given the presence of intercellular desmosomes and positive staining for P63, cytokeratin (CK)-7 and CK5/6, and negative staining

Figure 3 Bronchoscopy image showing ulcer and bronchial-oesophageal fistula.

Figure 4 Bronchoscopy image showing ulcer and bronchial-oesophageal fistula.

for thyroid transcription factor (TTF)-1, CK-20, CK-10, CK14 and synaptophysin. When studying cells of pulmonary origin, it is important to remember that squamous differentiation is identified by keratinisation and/or formation of intercellular bridges. Both features are specific for squamous cell differentiation and are not seen in other tumour types. While these features are readily observed in well-differentiated tumours, they may be difficult to appreciate or absent in poorly differentiated tumours, especially in small biopsy samples. In such cases, an immunohistochemistry panel including P63, CK5/6, TTF-1 and CK-7 may be helpful, with positive staining for P63 and CK5/6, and concurrent lack of staining for TTF-1, supporting squamous differentiation.⁵ On the other hand, pulmonary adenocarcinoma is differentiated from squamous cell carcinoma by being typically positive for CK-7 and TTF-1, and negative for p63 and CK5/6.⁶

Another differential considered was oesophageal cancer. The patient had a history of alcohol and tobacco abuse, both of which are risk factors for the development of squamous cell carcinoma of the oesophagus. Generally speaking, oesophageal cancer may be easily distinguished from lung cancer on morphology; these tumours resemble their counterparts in the skin and show varying degrees of squamous differentiation with extensive keratinisation. The immunohistochemical profile differs from squamous cell of the lung due to positivity for CK-10+ and CK-14+, and negativity for CK-7 and CD-20.⁷⁻¹⁰

Benign conditions causing fistula are less common and include infections such as tuberculosis, syphilis, histoplasmosis, actinomycosis and candidiasis.^{11 12} During our patient's hospital course, several blood and sputum cultures were collected, and results were negative for acute fungal infections. At the time of the bronchoscopy, a bronchoalveolar lavage was performed, with microscopic analysis revealing 2+ white count cells, rare budding yeast, absent pseudohyphae and no evidence of pneumocystis organisms or viral inclusions. Rare groups of markedly atypical epithelial cells were noted, highly suspicious for carcinoma with a background of bronchial cells, squamous cells and fibrinoinflammatory debris.

TREATMENT

Initially, the patient was treated for an acute bilateral pneumonia, which required broad spectrum antibiotics including intravenous vancomycin and Piperacillin/Tazobactam. Later, the patient developed profound hypoxemia despite 100% FiO₂, PEEP of 18 and 40 ppm of nitric oxide. On day 2 of admission, and despite all interventions, including systemic glucocorticoids, he developed ARDS requiring veno-veno extracorporeal

membrane oxygenation (ECMO). Hours after ECMO placement, the patient started experiencing endotracheal tube air leaks, initially thought to be secondary to tube defects or positional changes after the surgical procedure. This new finding prompted further investigations including bronchoscopy.

After the diagnosis of trachea-oesophageal fistula was made by bedside bronchoscopy, an upper endoscopy was performed due to persistent bleeding by the endotracheal tube; erosive gastritis was found with confirmation of the TOF, so an oesophageal stent was placed and total parenteral nutrition was started, and plans were made to place an airway stent later during the day, but our patient rapidly deteriorated due to multiple aspirations and the significant acute inflammatory reaction that subsequently ensued, and he progressively became hypotensive, requiring intravenous norepinephrine; he developed severe acidosis and acute kidney injury with an increase in creatinine from 0.8 to 4.0, ultimately requiring dialysis. As a last resource, the possibility of double-lumen intubation was considered, to reduce further lung aspirations, but at this time the family wanted a more conservative approach and comfort measures were established. Overall, the patient completed a cycle of broad spectrum antibiotics, aggressive management for ARDS including ECMO and management of clinical complications secondary to the trachea-oesophageal fistula.

OUTCOME AND FOLLOW-UP

After the results of the biopsy from the trachea-oesophageal fistula revealed a poorly differentiated carcinoma of the lung, thoracic oncology was consulted and a limited staging work up took place with CT of the abdomen reporting possible metastasis to the omentum. The patient's clinical status precluded the possibility of systemic chemotherapy or radiation. Several conversations were held with the family regarding low possibilities of recovery. The patient ultimately expired on the fifth day of admission after his family decided to withdraw further support in view of his terminal diagnosis and unresectable lung cancer.

DISCUSSION

Malignant TOF is a serious complication of thoracic malignant diseases and is more common in oesophageal cancer than in lung cancer.^{1 13} The largest study evaluating patients with malignant TOF reported an incidence of 0.16% in 5714 patients with lung cancer.¹⁴ Some patients can present with weeks of chronic cough due to microaspirations, but others can exhibit an acute and dramatic presentation. While evaluating our case, we noted that our patient had chronic cough for several days and was treated with oral antibiotics without improvement, revealing the progressive course of his disease. Recurrent respiratory infections are common and malnutrition leads to rapid deterioration. Life expectancy is estimated at about 6 weeks without proper and prompt treatment.³ When evaluating patients with possible TOF, it is important to collect all the information regarding past treatments as a majority of the patients have a history of chemotherapy or radiation for the treatment of oesophageal cancer or other malignancies of the head and neck. This was one of the unique characteristics of our case: the initial presentation of his malignancy, with no history of chemoradiation or recent procedures involving the upper airway or gastrointestinal tract.

Rapid diagnosis is imperative to prevent soilage of the tracheobronchial tree and rapid progression to respiratory failure. Bronchoscopy should be performed promptly if a fistula is suspected, followed by upper endoscopy. Radiological examinations are only helpful for initial diagnosis in the presence of

suspicious lung infiltrates due to aspiration or operational planning in medically stable patients.

The most common management of malignant TOF is palliative, aimed at maximising quality of life. Therapeutically, the goal should be restoring the patency of the trachea and enabling the patient to be nourished. Surgery is usually considered inappropriate in malignant TOF, as the patients tend to be in poor performance status and near the end of their lives.¹⁵ Airway and oesophageal stenting are safe procedures and beneficial for symptomatic relief. Some papers report high success rates in double stenting.¹⁶ Our patient received an oesophageal stent, but his clinical status and his family decision to move to comfort measures did not allow the placement of the airway stent to complete the double stenting procedure.

TOFs in ventilator-dependent patients present difficult management problems. When airway pressure increases, part of the delivered tidal volume may be lost through the tracheal defect, resulting in a dramatic decrease in alveolar ventilation with CO₂ retention. Delivering larger tidal volumes is usually not effective, since this requires higher inspiratory pressures, with resulting greater airleak and prolonged inspiratory times. The use of high frequency jet ventilation may be of value in this situation, as it can decrease mean airway pressure and thus reduce the amount of gas lost through the fistula. Additional benefit is derived from deflation of the endotracheal tube cuff, relieving pressure on the damaged mucosa.^{17 18} In our case, the diagnosis of TOF was performed after the patient was placed in ECMO; however, it is important to discuss how mechanical ventilation can improve or worsen the clinical course of patients with TOF.

Regarding the diagnosis of the primary neoplasia, immunohistochemistry played an important role in this case. Lung cancer can be differentiated from oesophageal cancer on the basis of immunoreactivity to a number of markers. The former is typically immunoreactive to CK-7, CK-5/6, CK-20 and TTF-1⁷⁻¹⁰ while the latter stains positively for CK-10 and CK-14, and negatively for CK-7 and CK-20. Additional microscopic characteristics can help differentiate between the subtypes of lung cancer, with squamous cell carcinoma having a unique keratinisation pattern and the presence of intercellular desmosomes. While the subtype of lung cancer did not change the treatment plan in our patient due to his poor clinical status, in other patients with stable disease, differentiating between histological subtypes can help determine the best chemotherapeutic agents for the patient.

This case shows that neither radiation, chemotherapy nor advanced disease are necessary preconditions for TOF formation. In patients with high oxygen requirements despite all therapeutic measures, it is necessary to include TOF in the differential diagnosis, as early treatment can increase life expectancy from days to months.

Learning points

- ▶ Lung cancer can present in different and sometimes very dramatic ways; malignancy should always be in the differential diagnosis when treating patients with persistent and extensive pneumonia, and history of tobacco abuse.
- ▶ Early detection of tracheobronchial fistula can improve a patient's survival from days to months.
- ▶ Even though a large percentage of the cases of tracheobronchial fistulas present as a consequence of chemotherapy and radiation, they can also be the initial presentation of lung cancer.

Contributors ND, CB and SS were involved in the care of the patient and preparation of the case report. LS was involved in the preparation of the case report.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Rodriguez AN, Diaz-Jimenez JP. Malignant respiratory-digestive fistulas. *Curr Opin Pulm Med* 2010;16:329–33.
- Grillo HC. Acquired tracheoesophageal and bronchoesophageal fistula. *Surgery of the Trachea and Bronchi* 2003;341–56.
- Reed MF, Mathisen DJ. Tracheoesophageal fistula. *Chest Surg Clin N Am* 2003;13:271–89.
- Ozturk O, Koksall D, Emri S. Tracheoesophageal fistula in a treatment naive patient with lung cancer. *Tuberk Toraks* 2014;62:174–6.
- Nicholson G, Gonzalez D, Shah P, et al. Refining the diagnosis and EGFR status of non-small cell lung carcinoma in biopsy and cytologic material, using a panel of Mucin staining, TTF-1, cytokeratin 5/6, and P63, and EGFR mutation analysis. *J Thorac Oncol* 2010;5:436–41.
- Yatabe Y, Mitsudomi T, Takahashi T. TTF-1 expression in pulmonary adenocarcinomas. *Am J Surg Pathol* 2002;26:767–73.
- Wong HH, Chu P. Immunohistochemical features of the gastrointestinal tract tumors. *J Gastrointest Oncol* 2012;3:262–84.
- Chu PG, Lyda MH, Weiss LM. Cytokeratin 14 expression in epithelial neoplasms: a survey of 435 cases with emphasis on its value in differentiating squamous cell carcinomas from other epithelial tumours. *Histopathology* 2001;39:9–16.
- Chu PG, Weiss LM. Expression of cytokeratin 5/6 in epithelial neoplasms: an immunohistochemical study of 509 cases. *Mod Pathol* 2002;15:6–10.
- Chu P, Wu E, Weiss LM. Cytokeratin 7 and cytokeratin 20 expression in epithelial neoplasms: a survey of 435 cases. *Mod Pathol* 2000;13:962–72.
- Lim KH, Lim YC, Liam CK, et al. A 52-year-old woman with recurrent hemoptysis. *Chest* 2001;119:955–7.
- Aggarwal D, Mohapatra PR, Malhotra B. Acquired bronchoesophageal fistula. *Lung India* 2009;26:24–5.
- Fitzgerald RH, Bartles DM, Parker EF. Tracheoesophageal fistulas secondary to carcinoma of esophagus. *J Thorac Cardiovasc Surg* 1981;82:194–7.
- Martini N, Goodner JT, D'Angio GJ, et al. Tracheoesophageal fistula due to cancer. *J Thorac Cardiovasc Surg* 1970;59:319–24.
- Simoff MJ, Lally B, Slade MG, et al. Symptom management in patients with lung cancer. Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143(5 Suppl):e455s–97s.
- Lutz F, Edith T, Heinz S, et al. Management of malignant esophagotracheal fistulas with airway stenting and double stenting. *Chest* 1996;110:1155–60.
- Payne DK, Anderson WM, Romero MD, et al. Tracheoesophageal fistula formation in intubated patients. Risk factors and treatment with high-frequency jet ventilation. *Chest* 1990;98:161–4.
- Carlson GC, Ray C Jr, Pierri MK, et al. High-frequency jet ventilation: theoretical considerations and clinical observations. *Chest* 1982;81:350–4.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow