Author’s response to reviews

Title: Postpneumonectomy-like syndrome due to bronchial carcinoid: a unique case report

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Author’s response to reviews:

November 10, 2018

Dear Editors,

RE: “Response to reviewers and submission of revised manuscript: PULM-D-18-00462
Postpneumonectomy-like syndrome due to bronchial carcinoid: a unique case report”

We thank all reviewers for their constructive comments and suggestions which have been very helpful in improving our manuscript. All the comments we received have been answered and we present our reply to each of them separately.

I would also like to inform you that a fully completed 'Request for change in authorship form' will be sent to your editorial office within the next days. Two authors, Dr. Rodoula Tringidou and Dr. Ioannis N. Vamvakaris who were not originally included on the initially submitted
manuscript are now added. Both Dr. Rodoula Tringidou and Dr. Ioannis N. Vamvakaris, pathologists, performed and interpreted the histopathological examinations that have been added to the revised manuscript, as requested by reviewers.

We hope that these changes to the manuscript will facilitate the decision to publish this study in BMC Pulmonary Medicine.

Yours faithfully,

Athanasios Konstantinidis, MD, PhD, on behalf of co-authors

Below, we present our answers to the specific comments, which will also cover the consequent changes made in the manuscript.

Udit Chaddha MBBS (Reviewer 1): General Comments

The authors present an interesting case which they do well to describe clinical details of. However, some issues remain unclear to me, which I have addressed in my comments.

Major Comments

- Why does this case represent a post-pneumonectomy "syndrome"? PPS usually involves airway +/- esophageal compression/ narrowing/ stretching from mediastinal shift. In this case there was no compromise of the right sided airways or the esophagus. While some right lung hyperinflation and herniation to the left is seen, this likely did not even produce symptoms as the patient was asymptomatic post-pneumonectomy even though the CT remained unchanged. Please clarify this issue and provide a short explanation in the discussion section for the readers.

We expanded the discussion on this point and the following text has been added or modified in the discussion section:

“The fact that the obstructed lung was the left one, explains the subtle symptoms of the patient as it is well reported that leftward shift of the mediastinum produces smaller anatomic and physiologic changes as the translocation of the heart and major vessels is smaller. Moreover, these changes in our patient developed gradually overtime in a young and otherwise healthy individual thus giving her the time to smoothly adapt to the new situation. Previously reported cases of postpneumonectomy syndrome after pneumonectomy demonstrated a wide clinical spectrum ranging from absence of symptoms, as in our patient, to rapidly progressive shortness of breath [1]. In addition, not all patients with extreme mediastinal shifts observed in large series of pneumonectomies for cancer in adults require symptomatic treatment [2]. However,
mediastinal repositioning remains a valid surgical option if our patient develops symptoms or signs of bronchial or esophageal compression and stretching in the future”.

Bibliography


Case presentation, 3rd paragraph: For better understanding for the readers, please devote a couple of lines here to elaborate the rationale to proceed with a pneumonectomy rather than a more parenchymal sparing surgery or even bronchoscopic resection (as it was TC), in a patient who is only 25 years old.

These very important questions are discussed in the new-written discussion section:

“We proceeded with surgery rather than bronchoscopic resection of the tumor (EBT), for two reasons. Firstly, chest CT scan showed a purely intraluminal growth of the tumor, which was confirmed by final pathology, and the mass started 2.8 cm distal to the main carina. However, tumor size was large enough, measuring 4.4×2×2.8 cm, and infiltrated the periphery of the main bronchus on chest CT scan and on final pathology. Secondly, biopsies taken during initial bronchoscopy showed a high Ki67 index, suggestive of an atypical carcinoid. We thus decided that the patient was not eligible for EBT, as this modality may have left substantial tumor behind. Our preoperative plan is supported by the findings of a large cohort of one hundred and twenty-five patients with a diagnosis of bronchial carcinoid who underwent endobronchial treatment [1]. In this cohort, no patient with a tumor diameter $\geq$20 mm was successfully treated with EBT, and the authors of that study recommended that these patients should be directly referred for surgery.

Given the young age and the rather limited pre-surgical pulmonary function of our patient (pre-surgical FEV1: 1.51 lit [44% pred.]), a parenchymal-sparing surgery, such as left main bronchus resection and reconstruction, along with nodal dissection might have been the ideal surgical treatment. However, a left pneumonectomy rather than a parenchymal sparing surgery was performed because chest CT scan showed infiltration of the periphery of the left main bronchus by tumor, which would not have allowed reconstruction of the left main bronchus and reaeration of the atelectatic lung because there was no free margin adequacy. Infiltration of distal main bronchus was subsequently confirmed by final pathology”.

Bibliography

Case presentation, 4th paragraph:

* "Spirometry and static lung volumes 12 months after surgery were as follows:β¦" Also mentioning the pre-operative values (if available) to ensure that she would be a good pneumonectomy candidate would be more informative, in the previous paragraph.

Pre-operative spirometry was as follows: FEV1: 1.51 lit (44% pred.), FVC: 1.54 lit (39% pred.), FEV1/FVC: 98%. Spirometry and static lung volumes 12 months after surgery were as follows: FEV1: 1.93 liters (58% predicted), FVC: 2.34 liters (61% predicted), FEV1/FVC: 82%, TLC: 3.28 liters (63% predicted), RV/TLC: 118% predicted. Although spirometry appears to be significantly improved after surgery, spirometry before surgery triggered fits of coughing and therefore preoperative values might not be representative.

* 6th line: What tumor markers are you "referring to? Please elaborate. ?

The following has been added to the manuscript:

“Plasma chromogranin A measurement has been carried out every six months”.

* "The patient has been asymptomatic for the last 16 months after surgeryβ¦" The line seemed misplaced. Please move to the end of the paragraph.

Done.

* Please elaborate on the what exact follow-up was carried out and is planned? E.g. CT at 3-6 months and then annually, and bronchoscopy in x years or earlier if triggered by imaging or symptoms.

We have added the following in the case presentation section:

“Postsurgical follow-up has included the following: Initial chest CT scan was carried out two months after surgery. Parathyroid hormone (PTH) and prolactin levels were within normal limits one year after surgery. The following investigations were carried out at 6 months and then every 6 months for the first 5 years: Chest CT scan, abdominal ultrasound, chromogranin A measurement and standard laboratory testing including complete blood count, renal function, liver function, calcium and glucose. Abdominal CT scan and fiberoptic bronchoscopy were carried out one year after surgery and then will be carried out annually for the first 5 years. Bronchoscopy would be performed earlier for any symptoms or imaging findings suggestive of local progression”.

Minor Comments
Case presentation, 1st line: delete "of our hospital", add 'ED' in parenthesis after emergency department: "(ED)"

Done.

Case presentation, 2nd paragraph, line 1 and 2: Expand CXR - chest x-ray. Expand CT - computerized tomography. (since these two are being used for the first time). Correct the spelling of "tracheobronchial"

Done.

Figures

Figure 1a: delete "initially" and "consolidation"

Line 3: Change 'toward' to 'towards. Delete "hemithorax"

"The lung parenchyma at the level of the left upper hemithorax (white arrow) represents overexpanded right lung herniated into the left upper hemithorax" - I don't think this can be said with confidence based off just the chest x-ray.

We agree with the Reviewer and have reformulated figure legend 1:

“Fig. 1. a. Chest radiograph (postero-anterior view) showing opacification of the left middle and lower lung zone. Tracheal deviation towards the left is also evident; (black arrow). b. Lateral chest radiograph”.

Danai Khemasuwan, MD, MBA (Reviewer 2): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

This is a quite unique case of postpneumonectomy-like syndrome due to endobronchial carcinoid which led to complete obstruction of left main stem and total atelectasis of left lung. The manuscript is well-written and the authors have reviewed several relevant articles. I have several questions for the authors.

1. Although, open left pneumonectomy and lymph node dissection seems to be an appropriate treatment for this patient. Did the authors attempt to perform any endobronchial treatment such as rigid bronchoscopy or ablative therapy? This part should be added in the discussion section.
To clarify our therapeutic approach to the patient we have added the following text in the discussion section:

“We proceeded with pneumonectomy and systemic nodal dissection, rather than bronchoscopic resection of the tumor (EBT), for two reasons. Firstly, chest CT scan showed a purely intraluminal growth of the tumor, which was confirmed by final pathology, with the mass starting 2.8 cm distal to the main carina. However, tumor size was large enough, measuring 4.4×2×2.8 cm, and infiltrated the periphery of the main bronchus on chest CT scan and on final pathology. Secondly, biopsies taken during initial bronchoscopy revealed an atypical carcinoid. We thus decided that the patient was not eligible for EBT, as this modality may have left substantial tumor behind. Our preoperative plan is supported by the findings of a large cohort of one hundred and twenty-five patients with a diagnosis of bronchial carcinoid who underwent endobronchial treatment [1]. In this cohort, no patient with a tumor diameter ≥20 mm was successfully treated with EBT, and the authors of that study recommended that these patients should be directly referred for surgery”.

Bibliography


2. In page 6, the authors mentioned "assessment of tumor markers for early detection of carcinoid" Please describe what are those tumor markers?

A new-written follow-up care plan was added and it is now clarified that plasma chromogranin A measurement has been carried out every six months.

3. In page 8, "Moreover, postpneumonectomy syndrome after left pneumonectomy usually present with less severe symptoms compared to those after right pneumonectomy". Any explanation on this phenomenon? Any use of objective parameters on measurement of symptoms?

We provide an explanation on this phenomenon and the following text has been added in the discussion section:

“The fact that the obstructed lung was the left one, explains the subtle symptoms of the patient as it is well reported that leftward shift of the mediastinum produces smaller anatomic and physiologic changes as the translocation of the heart and major vessels is smaller”.

Karishma Mehra (Reviewer 3): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.
1) Did she have any underlying parenchymal lung disease possibly pneumonitis which can be seen with bronchial carcinoid?

The patient had no evidence of parenchymal lung disease suggestive of diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH) based on chest CT scans.

2) What is the typical time to onset of post pneumonectomy like syndrome after the start of underlying lung disease?

Among seventy-three cases of postpneumonectomy syndrome in adults reported in the literature, the median interval between pneumonectomy and onset of symptoms was 2 years (range 1 month—49 years). Among four cases of postpneumonectomy-like syndrome involving patients with unilateral lung destruction due to previously treated severe parenchymal tuberculosis, one patient suffered from pulmonary tuberculosis 40 years earlier, one patient 30 years earlier, one patient 21 years earlier and the fourth patient 20 years earlier. We have to emphasize though, that the authors of those case reports do not provide sequential imaging studies, therefore, it is not known if those patients had additional volume loss in the affected lung over time. In a case involving a 44-year-old woman with Hodgkin’s lymphoma, the patient received chemotherapy and left mediastinal irradiation 12 years prior. Chest X-ray 10 years prior showed atelectasis of the left lower lobe and initial mediastinal shift. When she developed postpneumonectomy-like syndrome, the left lung was completely atelectatic and a solid lesion of 8 × 5 cm in the upper part of the left lung was found. Biopsy diagnosed a recurrence of Hodgkin’s lymphoma and repeat chemotherapy improved the respiratory symptoms. In another case involving a 70-year-old woman, the patient had a previous right upper lobectomy for stage I lung cancer 15 years prior to developing postpneumonectomy-like syndrome, a wedge resection of the right lower lobe for a second primary lung cancer 9 years prior and radiation therapy for isolated right hilar lymph node metastasis 4 years prior. In the final case, a 45-year-old man with a history of C7 tetraparesis underwent a right lower lobectomy due to destruction of the lobe due to multiple episodes of pneumonia. Two months later she developed stridor and dysphagia and a chest CT scan revealed significant volume loss in the right middle and upper lobes due to retained secretions and significant dextro-rotation of the mediastinum with compression of the left main bronchus against the thoracic spine.

Based on the above, we have added the following to the manuscript:

“Among seventy-three cases of postpneumonectomy syndrome in adults reported in the literature, the median interval between pneumonectomy and onset of symptoms was 2 years (range 1 month—49 years) [1]. Among the seven cases of postpneumonectomy-like syndrome reported in the literature, the time between start of the underlying disease and the onset of postpneumonectomy-like syndrome ranged from two months to thirty years. The longest time interval involved patients with long-standing destructive pulmonary tuberculosis, however, in those cases the authors have not provided either initial or sequential imaging studies, therefore, it
is not known if those patients had gradual volume loss in the affected lung over time or not. The time between start of carcinoid and the diagnosis of the syndrome in our patient is unknown, since the patient had not previously undergone chest imaging studies.”

Bibliography


3) Page 5 Line 7- need correction of word tracheobronchial.

Done.

4) In pathology images can you confirm chromogranin staining

Four pathology images have been included in the manuscript. Two of them demonstrate diffuse and intense immunoreactivity to synaptophysin and CD56.

Figure legend 4 in the manuscript reads as follows: “Fig. 4. Histology of bronchial atypical carcinoid tumor. a. Small rounded uniform cells and highly vascularized stroma are seen. Bronchial epithelium on the left appears intact. (hematoxylin-eosin). b. Strong synaptophysin expression in tumor cells. c. Bright CD56 expression in tumor cells. d. Ki67 immunostaining in tumor cells was approximately 10% (original magnifications x 40 [A through D]).”

5) Outcome - how long after surgery did her symptoms resolve?

Patient reported resolution of her mild exertional dyspnea upon discharge from hospital, at day 7 postsurgery, indicating that it her dyspnea was most probably due to the shunt produced by the completely collapsed left lung.

6) If she already had hyperinflation and deviation of right lung, did you consider placement of prosthesis after her pneumonectomy?

We have added the following in the discussion section:

“Although we considered implantation of prosthesis in the left mediastinum to maintain mediastinal position after pneumonectomy, we have not proceeded to surgical correction since the patient has remained asymptomatic with no evidence of bronchial or esophageal compression or stretching on repeat chest CT scans and bronchoscopy. However, mediastinal repositioning remains a valid surgical option if the patient develops symptoms or signs of bronchial or esophageal compression and stretching in the future.”
Haala Rokadia, MD (Reviewer 4): This manuscript is a well written case report and review of a young patient with complete endobronchial obstruction of the L mainstem bronchus from bronchial carcinoid and subsequent imaging of post-pneumonectomy like syndrome. This manuscript would be acceptable for publication after the revisions below.

The following are my comments:

1. This manuscript would be strengthened by the inclusion of labelled histopathologic images of the carcinoid tumor. (minor essential revision)

Four pathology images have been added in the manuscript. Two of them demonstrate intense immunoreactivity to synaptophysin and CD56 by the tumor cells.

The following figure 4 legend has been added: “Figure 4. Histology of bronchial atypical carcinoid tumor. A. Small rounded uniform cells and highly vascularized stroma are seen. Bronchial epithelium on the left appears intact. (hematoxylin-eosin). B. Strong synaptophysin expression in tumor cells. C. Bright CD56 expression in tumor cells. D. Ki67 immunostaining in tumor cells was approximately 10% (original magnifications x 40 [A through D])."

2. If possible, the addition of a labelled coronal image of the chest CT should be added to the CT images. (minor essential revision)

This is a very useful recommendation, since the two coronal chest CT images added to figure 1, demonstrate very clearly the extreme mediastinal deviation and substantial herniation of the right lung into the left hemithorax.

3. Addition of a short review of atypical carcinoid in the discussion section would be helpful for the readers. (discretionary revision)

We have added the following in the introduction section:

“Lung carcinoids are considered rare tumors with an annual incidence comprising between 2.3 and 2.8 cases per 1 million people; they include 20% to 25% of all carcinoid tumors throughout the body but account to only 0.4% to 3% of all primary lung cancers [1]. Typical carcinoids account for the majority of carcinoid tumors and are approximately four to eight times more frequent than atypical carcinoids [2]. Lung carcinoids are the most common primary lung neoplasm in children and late adolescents, with typical carcinoids prevailing by far over atypical carcinoids [3]. Carcinoid syndrome is found in 2–5% of pulmonary carcinoids, most often when liver metastases are present. Pulmonary carcinoids may be rarely associated with MEN1 syndrome (1%–5% of patients), while Cushing’s syndrome is found in 1%–6% of patients [3]. Approximately 75% of patients with carcinoid tumors present with central tumors and symptoms of cough, hemoptysis, wheeze, recurrent pneumonia or chest pain [2]”.
We have added the following in the discussion section:

“We have added the following in the discussion section:

“According to the last WHO 2015 classification of tumors of the lung, pleura, thymus and heart [4], neuroendocrine tumors of the lung are neuroendocrine epithelial malignancies and are separated into 4 major categories: small-cell lung carcinoma (SCLC) and large-cell neuroendocrine carcinoma (LCNEC) (which are high-grade neuroendocrine tumors) and typical carcinoid tumor (TC) and atypical carcinoid tumor (AC) (which are considered to be low- and intermediate-grade malignant tumors, respectively). Neuroendocrine differentiation of carcinoids is established by immunohistochemical identification of secreted and cytoplasmic products such as synaptophysin, neuron-specific enolase, and chromogranin [5].

Carcinoid tumors are divided into two subcategories: typical carcinoid tumors with <2 mitoses per mm2 and lacking necrosis, and atypical carcinoid tumors with 2-10 mitoses per mm2 and/or foci of necrosis. The Ki-67 antigen identifies proliferating cells spanning from G1 to M phase and is valuable in biopsy samples with crush artifact, where mitotic index is difficult to assess, and may play a role in predicting prognosis [3]. The recent WHO 2015 classification mentions that a tumor with carcinoid-like morphology has a low labelling index (<10 – 20%). However, although Ki-67 labelling index cut-off values ranging from 2.5% to 5.8% have been proposed in the literature, the utility of this marker to discriminate typical carcinoid from atypical carcinoid to predict prognosis is not established [4,6]. However, at the individual patient level, none of these features enables a reliable prediction of clinical outcome as tumor recurrence was found to correlate significantly not only with the carcinoid histotype and mitotic index, but also with tumor location, necrosis, tumor vascular invasion and synchronous mediastinal nodal metastasis [7]. Typical carcinoids rarely metastasize and exhibit a 5-year survival rate ranging between 97% and 100%, whereas patients with atypical carcinoids have a greater tendency to present with lymph nodal involvement and distant metastases, usually to liver and bone, and have a 5-year survival rate varying from 25% to 70% [1].”

Bibliography


Please check the manuscript for spelling/grammatical errors.

Checked.