Case Report

Recurrent chest infections in two young non-smoker men

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Abstract

Pulmonary mucinous cystic carcinomas are rare salivary gland type carcinomas of the lung. They form part of a wide spectrum of mucin secreting glandular mixed type tumours. They comprise 0.1 – 0.2% of all lung tumours. They occur more frequently in young patients and present with cough or recurrent chest infections and therefore may be easily misdiagnosed. Since treatment depends fully on complete surgical resection early diagnosis is essential. Even with treatment the 10-year survival is quoted at 53%. We describe two cases of such rare tumours both of who underwent curative surgical resection. Both patients were younger than 35 years old and presented with recurrent chest infections. The patients were followed for up to eight years and the outcome recorded. A literature search confirms the occurrence in younger patients, who often present with pneumonias and that surgery is the only hope for cure.

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Introduction

Pulmonary mucinous cystic carcinomas are rare but highly malignant tumours. They form part of a wide spectrum of mucin secreting glandular mixed type tumours including mucinous cysts, mucoepidermoid carcinoma, multilocular cystic carcinoma, pseudomyxomatous pulmonary adenocarcinoma and colloid carcinoma.[1] The international association of lung cancer classifies this type of neoplasia as colloid adenocarcinoma.[2] They are salivary gland type carcinomas located within the airways accounting for 0.1 – 0.2% of all lung tumours and for less than 0.1% of all cancer deaths.[3]

Case 1

A 34-year-old male non-smoker with a past history of childhood asthma presented initially in 2007 with pneumonia that was successfully treated. One year later he presented with another chest infection that did not resolve for several weeks, leaving him with a persistent chronic cough (fig 1). CT Thorax showed a narrowed left lower lobe bronchus probably due to carcinoma (fig 2). The diagnosis was confirmed 18 months after the initial presentation with pneumonia. Bronchoscopy showed a white cystic and very vascular mass obstructing the lumen of the anterior segment of the left lower lobe but biopsies were inconclusive. Left lower lobectomy was performed, frozen section of the bronchial margin showed carcinoma and completion left pneumonectomy was performed during the same operative session. On formal histological examination the tumour was shown to be an adenoid cystic carcinoma with colloid laden cystic spaces and compact glandular spaces (fig 3, fig 4). The immunohistochemistry showed positivity for CD 117 and p40, while androgen receptors were focally positive. There was a faint and incomplete immunoreactivity for Her-2 in 20% of neoplastic cells. Malignant cells were present in the pneumonectomy resection margins at the left main bronchus. The tumour was low-grade and the

lymph nodes were tumour free. The patient received adjuvant chemo-radiotherapy. Three years later, metastases were detected in the ipsilateral pleura, contralateral lung and spleen. These were followed by multiple bone metastases and five and a half years following the pneumonectomy the patient passed away due to multiple metastases.

Case 2

A 28 year old male presented with 3 episodes of right lower lobe pneumonias during the previous four years. A CT thorax performed during his first pneumonia showed no tumour or obstruction of the right lower lobe bronchus. The second pneumonia, 4 years later, was investigated solely with a plain PA chest radiograph (fig 5). Upon presenting for the third time 6 months later another CT thorax was taken with contrast. This showed a soft tissue tumour at the origin of the right lower lobe bronchus obstructing the airway (fig 6, fig 7). This was confirmed at bronchoscopy. Biopsies showed squamous metaplasia but no malignancy. A right lower lobectomy was performed one month after diagnosis. Histology showed low-grade mucoepidermoid carcinoma of the lung (fig 8, fig 9). Complete resection was achieved yet post-operative adjuvant treatment was still given on recommendation of the multidisciplinary team. Yearly bronchoscopy and CT thorax have been performed for the past 9 years (since surgery) and no recurrence or metastasis has been detected.

Figure 1: *PA Chest x-ray showing spherical lesion obscured by left cardiac border. This is easily missed if clinical suspicion of tumour is low*

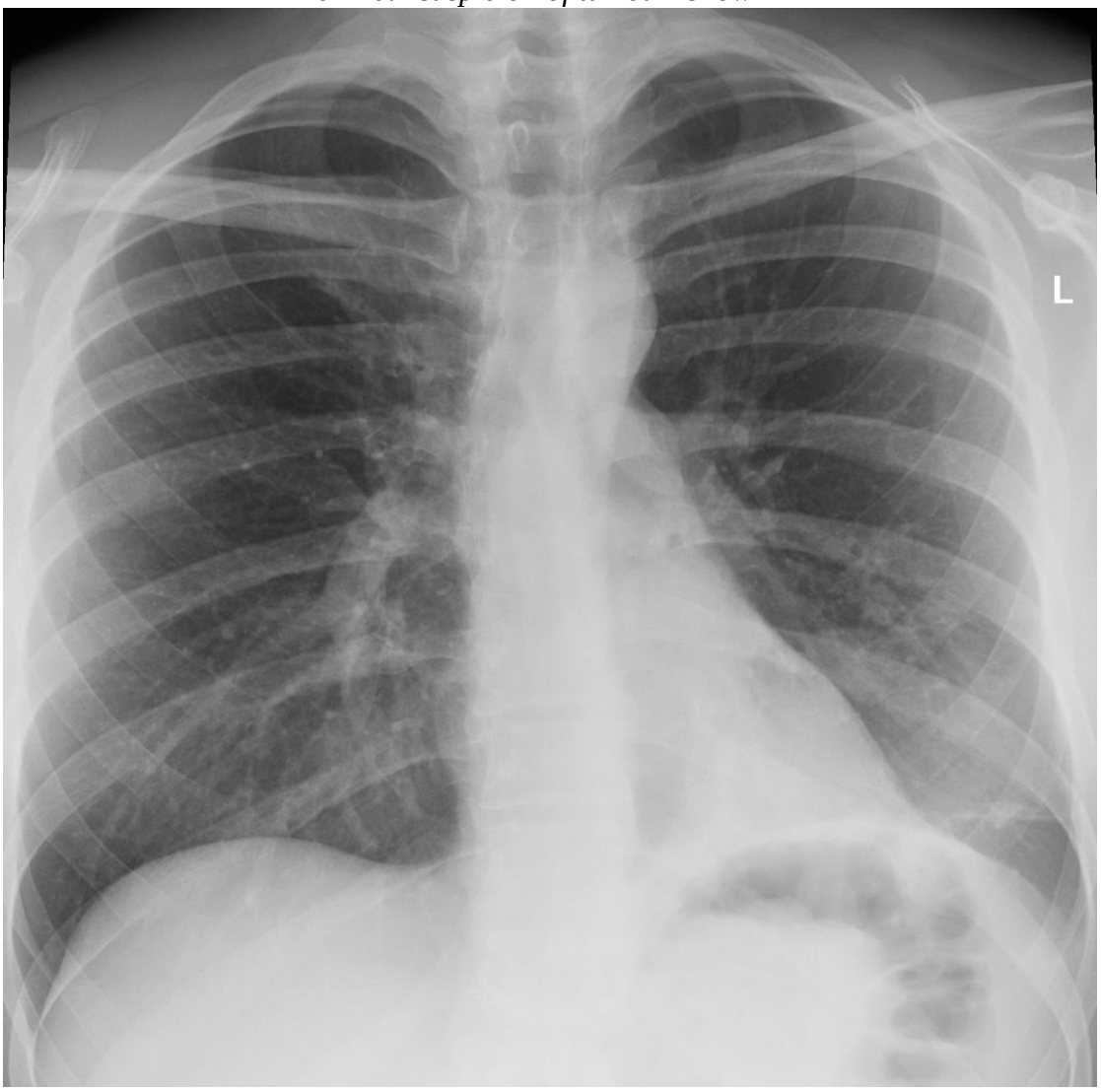


Figure 2: *CT with IV contrast showing the central lesion obscuring the left lower lobe bronchus*

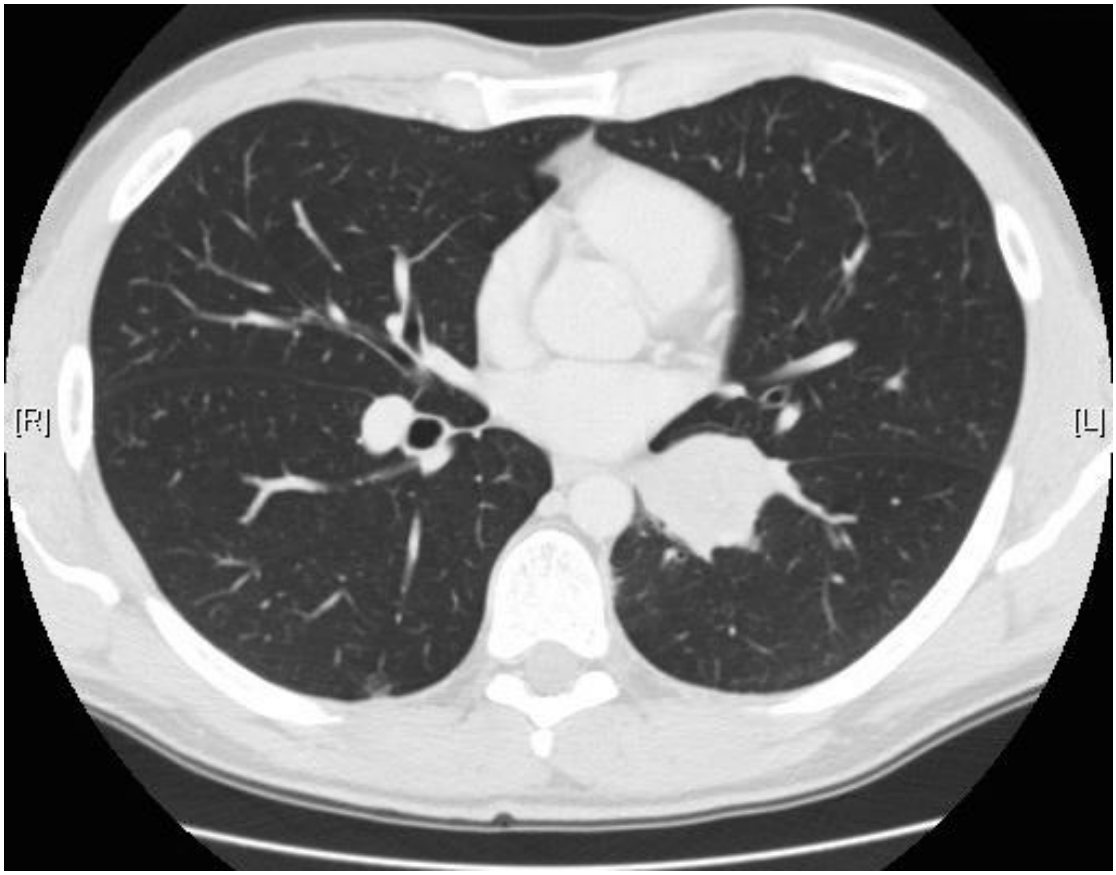


Figure 3: *Adenoid cystic carcinoma of the bronchus (H&E) X 10*

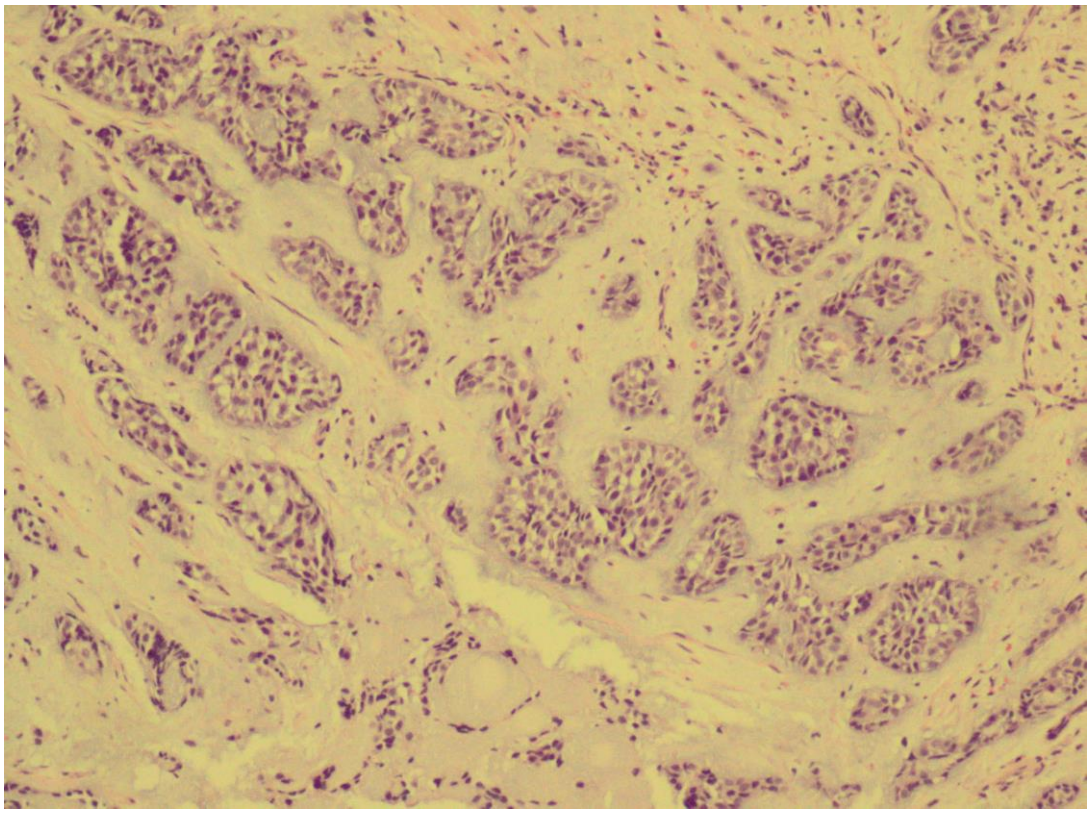


***Figure 4**: Colloid laden adenoid cystic carcinoma of the bronchus (H&E) X 10*

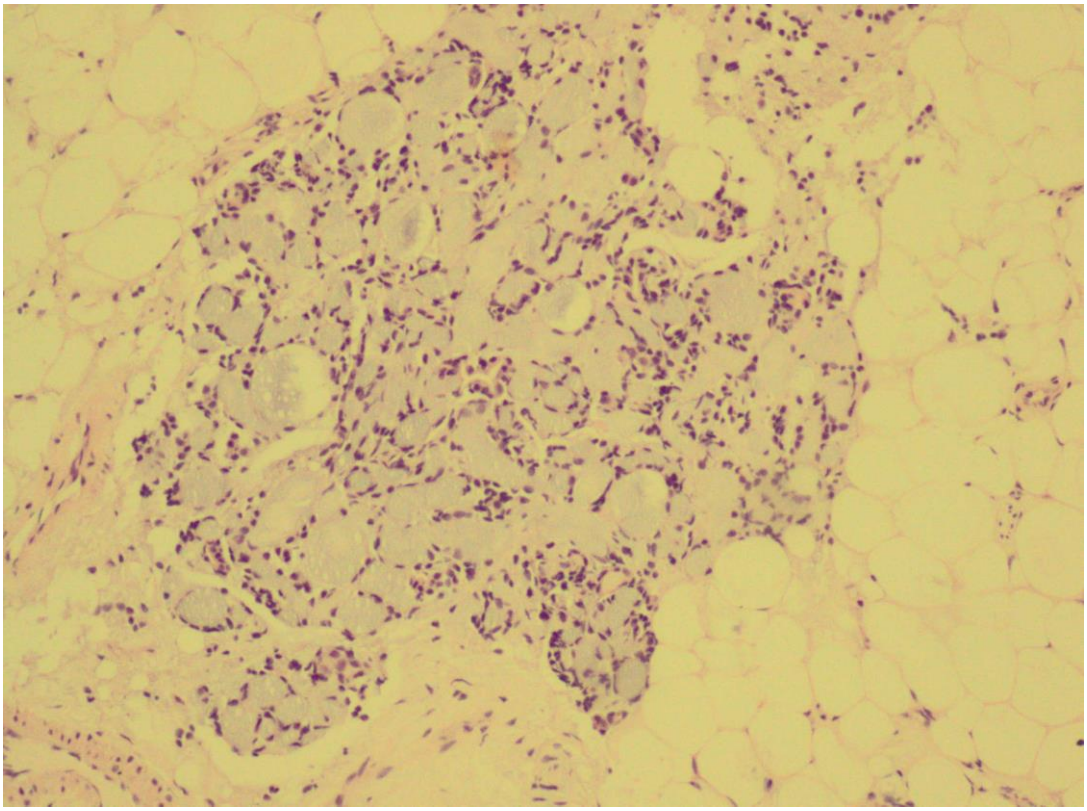


***Figure 5**: PA chest x-ray showing consolidation of pneumonia but no evidence of tumour*

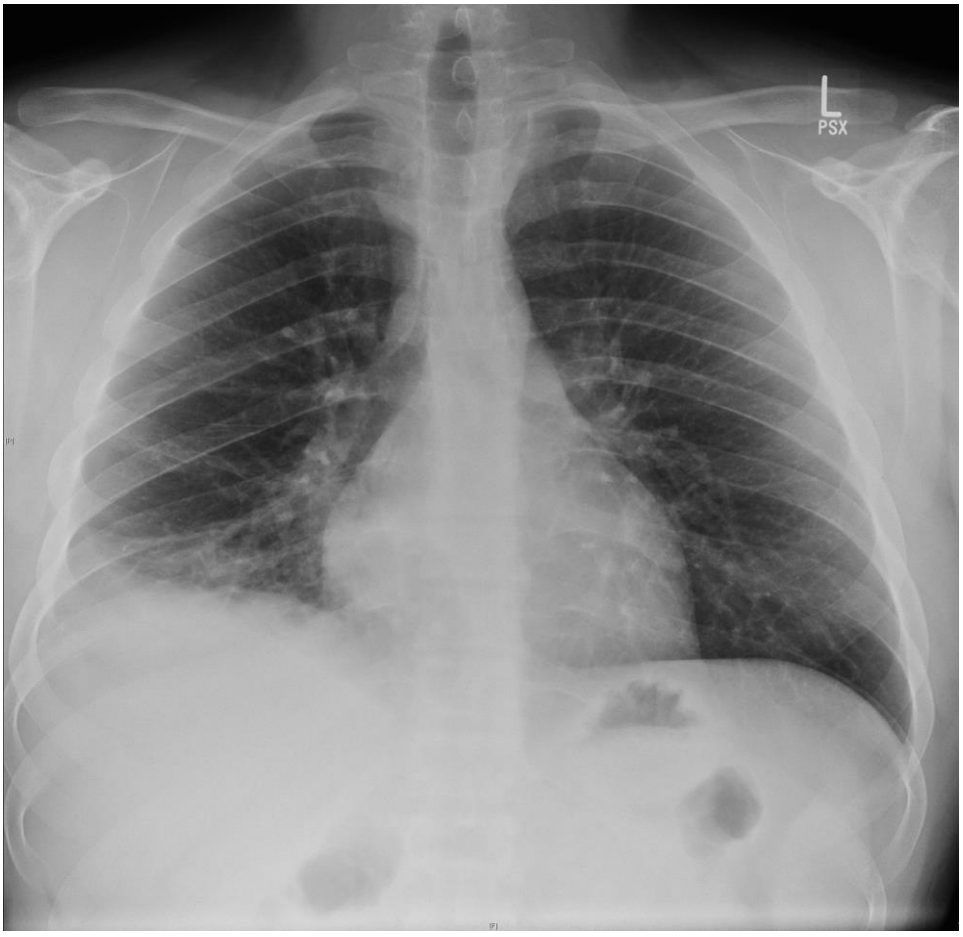


***Figure 6**: CT showing the tumour obstructing the right lower lobe bronchus*

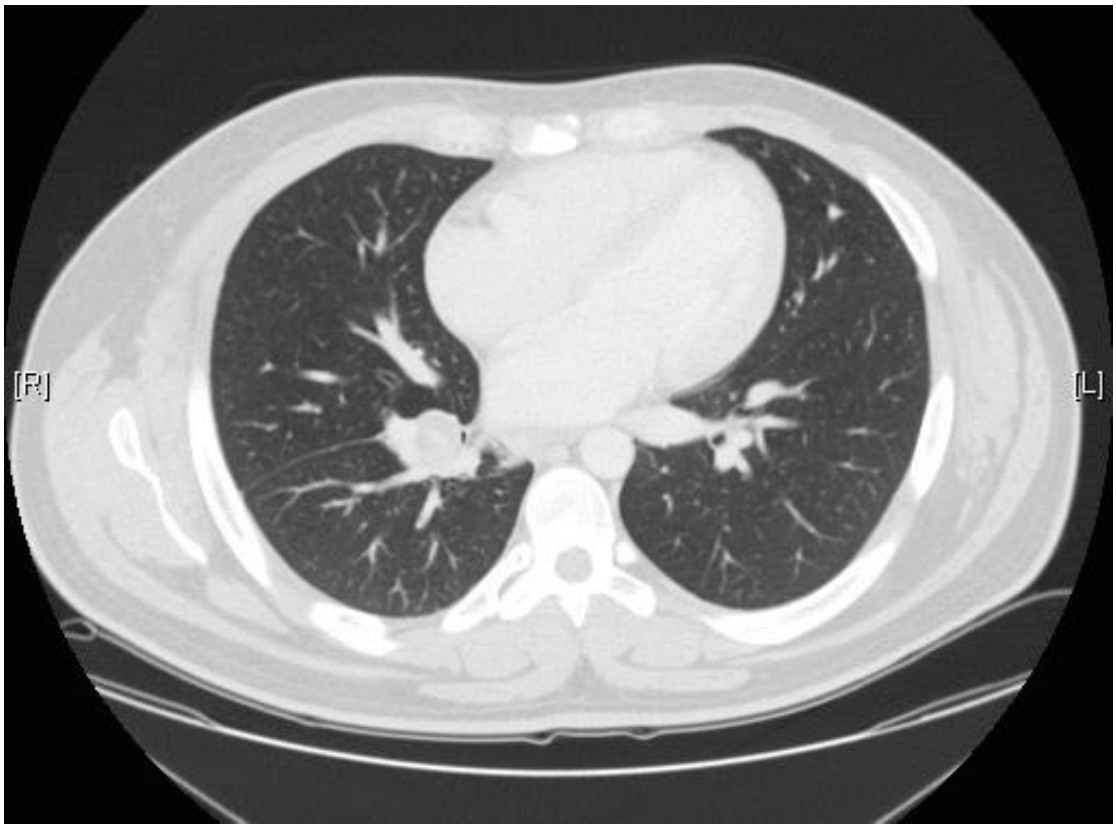


***Figure 7**: CT showing post-obstruction pneumonia of the right lower lobe*

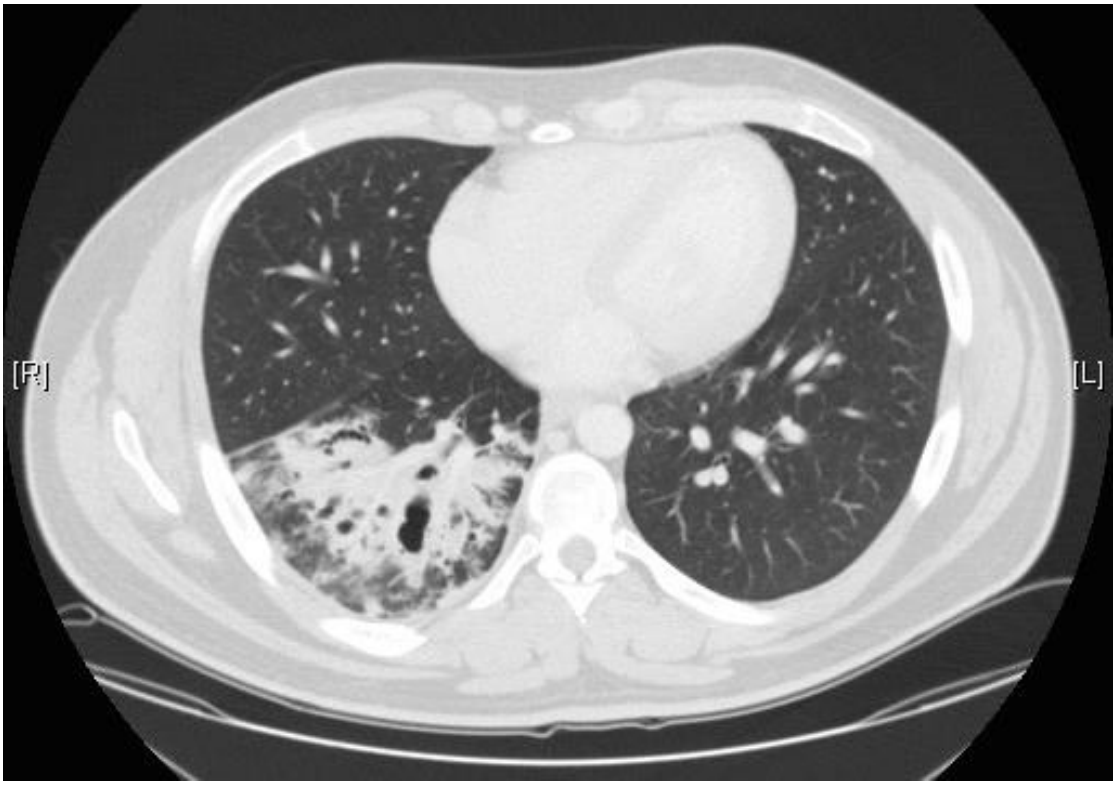


***Figure 8**: Mucoepidermoid tumour of the bronchus (H&E) X10*

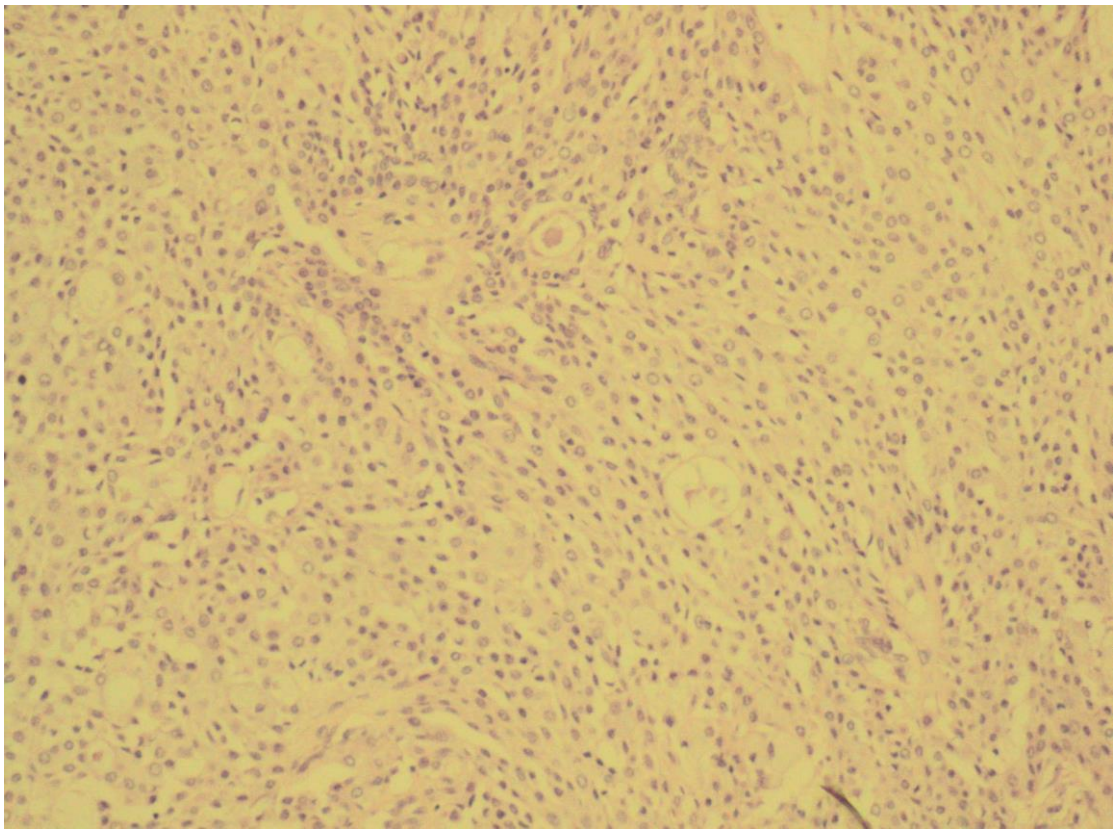
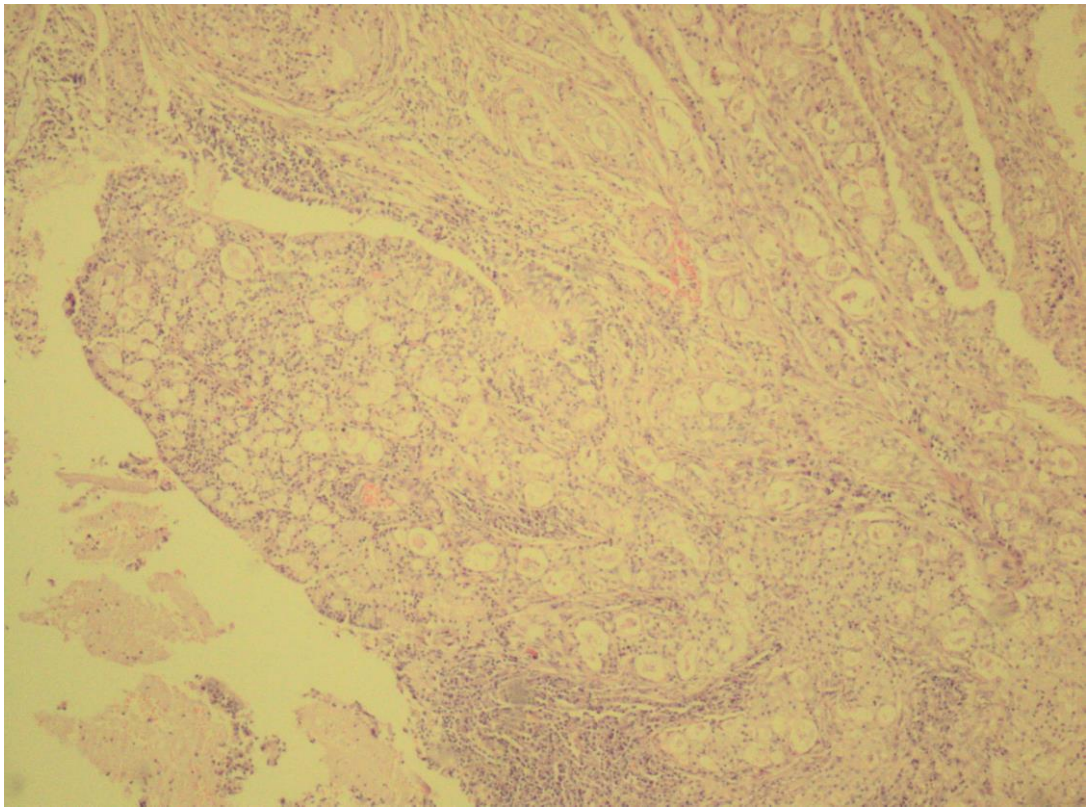


***Figure 9**: Glandular elements in mucoepidermoid carcinoma of the bronchus (H&E) X10*



Discussion

The first two cases ever documented were in 1952 by Smetana et al.[4] and by Liebow et al.[5] respectively. Both authors described the tumours as variants of cylindromas and as a subgroup of adenomas. These cases were mentioned as part of a series of pathological reports on lung lesions.

Mucoepidermoid carcinoma and adenoid cystic carcinoma both arise from salivary gland epithelial tissue. These tumours are more likely to arise in the upper third of the trachea contrary to squamous cell carcinoma that usually arises in the distal trachea however the two cases we are describing here were rare distal adenocystic carcinomas. It is even much rarer for these malignancies to occur in main stem bronchi as described in our cases.[6]

They present in younger patients irrespective of smoking habits. The symptoms may be very non-specific and varied. Our cases presented with cough and distal infections however the literature describes cases presenting with chest pain, shortness of breath, hoarseness, hyponatraemia and incidental findings in asymptomatic patients. Therefore these young patients may be easily under-investigated and on average 12 months would have elapsed from the first symptoms to the diagnosis.[7] In our cases the time to diagnosis was 18 and 10 months respectively conforming to that of other cases.

The tumour arises from bronchial glands and is made up of sheets of uniform cells containing glandular lumina. These tumours are identical to salivary gland tumours. Differentiating it from the more common ovarian or pancreatic mucinous cystic neoplasms may be possible with immunohistochemistry, as the pulmonary type is positive for CK7 and CK20.

It is mostly a low-grade, slow-growing tumour that spreads along the submucosa of the trachea or bronchus beyond that which is macroscopically apparent.[8] This explains the increased rates of positive margins, as occurred in one of our cases. Despite this, there is significant benefit in resecting tumours even if adequate margins cannot be achieved as the slow-growing nature of the tumour and the palliation provided by postoperative radiotherapy may result in long-term control.[9] Despite the response to radiotherapy and chemotherapy, surgical resection is the best way to achieve complete cure. The delay in diagnosis, for reasons mentioned above, will compromise the possibility of achieving complete resection. Local invasion beyond the airway is possible but rather than invading mediastinal structures it will push them aside. Local lymph node spread is also possible but less frequent than metastatic spread to the lungs or other distant organs. There is a rare subtype of these low-grade tumours that is highly malignant (grade III) and is prone to early metastatic spread and rapid local recurrence if margins are not clear.[10]

Chest x-ray may sometimes show the tumour,[11] however the gold standard imaging modality is CT scan. Using high resolution CT (HRCT) one can estimate the extent of airway involvement as well as the degree of airway obstruction and distal collapse and infection. Spiral CT with 3D reconstructions will help plan the extent of resection. MRI is not often used but may provide more information on longitudinal extension and on mediastinal infiltration. Lung function tests will clearly show airway obstruction with a flattened flow-volume loop, reduced forced expiratory volume in one second (FEV1) and a reduced peak expiratory flow rate (PEFR). These findings are not reversed with bronchodilators. Bronchoscopy is essential in diagnosing the type of tumour both visually and histologically. Biopsies of these tumours may be hazardous when in the trachea due to acute airway obstruction and bleeding. In our case both lesions were in the main bronchi or branches thereof and therefore biopsies could be performed safely.

Complete surgical resection is the only cure. Chemotherapy and radiotherapy may only play a role in low-grade tumours and will only offer prolongation of lifespan.[12] The type of resection depends greatly on the location of the tumours. The more common tracheal tumours require resection of the airway with primary anastomosis if sufficient length of trachea is available. Novel techniques are being perfected such as neotracheal reconstruction using free forearm full thickness flaps with autologous costal cartilage strips or even tracheal transplantation. However for lesions in more distal airways, such as the ones presented here, resection of the airway with lung salvage is not possible and lobectomy needs to be performed. Gao & Urbanski reviewed 66 cases operated for primary mucinous cystic neoplasms occurring in bronchi and all were treated with lobectomy, segmentectomy or wedge resection with good results.[8] Tumours located in main bronchi, as in one of the cases discussed here,

are amenable to sleeve resections in order to avoid pneumonectomy. As far back as 1980 Breyer *et al*. reported 5 cases operated for mucoepidermoid carcinoma; one underwent lobectomy, another tracheal resection with primary anastomosis and the other 3 received sleeve resections with primary re-anastomosis of the main bronchi.[13]

Even with treatment the 10-year survival is quoted at 53% for low-grade and 39% for high grade.[14] Even with complete resection 5-year survival is 80% for low grade and 31% in the rarer high grade.[12] Interestingly in those with complete surgical resection the 5-year and 10-year survival rates are identical. As in the case of our patients the one with complete surgical resection is well at 9 years whereas the one with positive margins died after 5 years. Local recurrence can occur many years after surgery. The main prognostic factor is lymph node involvement on intraoperative sampling and this should be routinely performed. Therefore these patients require long-term follow-up postoperatively.

Besides the larger case series mentioned above several other small series have been published. Nine case reports of 1 to 3 cases were reviewed and summarised in table 1.

In 1987, Yousem and Hochholzer described 58 cases taken from the Pulmonary and Mediastinal Pathology Registry, Washington between 1960 and 1986. 45 had low-grade tumours with an average age of 34.8 years. Submucosal infiltration was noted in 40 cases. All were resected surgically and one suffered lymph node metastasis, the rest remained disease free. High-grade tumours were present in 13 patients with an average age of 44.5 years. Overall 50% were smokers. All patients but one underwent surgical resection. That one patient was treated with radiotherapy only. Lymph node metastasis was present in 2 cases and both died of the disease, another 3 patients died of widespread metastasis. One patient had local recurrence, which was re-resected and survived.[15]

Table 1*: Series of case reports of patients with mucinous cystadenocarcinoma*

Author	Year	No. of Cases	Age	Presenting features	Surgery	Outcome in months (m)
Raza et al[16]	2009	1	67	Hyponatraemia	Unfit for surgery	n/a
Wynveen et al[1]	2008	1	75	Incidental finding	Lobectomy	Disease free at 24m
Hironori et al[17]	2003	1	42	Incidental finding	Lobectomy	Disease free at 24m
Moran et al[18]	2003	2	48, 61	Dyspnoea, Chest pain	Non-anatomical resections	Disease free at 12m Disease free at 12m
Jesse et al[19]	1984	1	66	Productive cough	Pneumonectomy	n/a
Klacsmann et al[20]	1979	2	39, 52	Cough, Incidental finding	Lobectomy, pneumonectomy	Disease free at 24m Disease free at 24m
Trentini et al [21]	1972	1	25	Dyspnoea, haemoptysis	Sleeve resection (+ve margins)	Died at 3m
Heilbrunn et al[22]	1972	3	22, 59, 60	Pneumonia, hoarseness, chest pain	Lobectomy, (+ve margins) radiotherapy,	Disease free at 6m Died at 24m Died at 12m
Kitada et al[11]	2011	1	60	Incidental finding	VATS lobectomy	Disease free at 9m

n/a = not available

Comparable to the literature our patients were young, average age of 31 years, and both were non-smokers. Smoking is not directly linked to these tumours and neither are environmental pollutants, however the link with lung cancers is present and therefore some influence may be present. Our patients lived in different parts of the island, one in a central town and the other by the sea. Both our patients are male but the literature shows no gender differences in prevalence.[23] They both presented with recurrent chest infections and both were potentially under investigated initially as commonly

occurs. Bronchoscopy gave plenty of visual information but histologically was ineffective. Both cases were of low-grade tumour and had not metastasised to lymph nodes or distant organs at the time of surgery. As discussed above the slow growing nature of this tumour created situations were positive margins were tolerated and local control was achieved with radiotherapy.[9] Our cases show the different outcome in cases with incomplete resection and hopefully encourage others to be more aggressive in achieving clear margins with more advanced techniques of sleeve resections and transplantation. Nonetheless even with positive margins our first case survived for over 5 years (3 years of disease free survival) and that is the reason why a long period of follow-up was essential before reporting these cases.

Learning Points

- Mucinous cystadencarcinomas are rare but highly malignant.
- They occur in patients who would be considered low risk; young patients who are non-smokers.
- They are asymptomatic or present with recurrent chest infections due to major airway obstruction.
- Chest x-ray and even CT may be misleading if infection obscures the tumour.
- A high index of suspicion is required; especially when a young healthy individual is getting recurrent pneumonia. Close follow-up is essential following infection to detect tumour that might have been hidden by infection.
- Early diagnosis and complete surgical resection offers a better chance of cure and therefore a respiratory physician should be consulted early for bronchoscopy and, if needed, the patient is then referred to a thoracic surgeon.

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