Bullous lung diseases as a risk factor for lung cancer - A case report

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Abstract

Introduction. A possible association between lung cancer and bullous lung disease has been suggested and recently supported by the results of genetic studies.

Case report. A previously healthy 43-year-old man, smoker, was diagnosed with bullous lung disease at the age of 31 years. He was followed up for 12 years when lung cancer (adenocarcinoma) was found at the site. In the meantime, he was treated for recurrent respiratory infections.

Conclusion. There is the need for active approach in following up the patients with pulmonary bulla for potential development of lung cancer.

Key words: lung neoplasms; risk factors; bronchopneumonia; diagnosis; tomography, x-ray, computed; disease progression.

Introduction

A bulla is a sharply demarcated, air-containing space of 1 cm or more in diameter that possesses a smooth wall of 1 mm or less thickness. Bullae may be large enough to compress the adjacent lung parenchyma and may occupy most of a lung. Bulla may be isolated or a part of diffuse emphysematous lung disease 1−3.

Previous reports have suggested that lung cancer may develop in patients with bullous lung disease 4, 5. Some of the reports provide retrospective data suggesting that bullous lung disease may predispose to the development of lung cancer in smokers 6, 7. It seems that lung cancer in this population occurs more frequently at younger age compared to general population. It may be worthwhile to target this group in an attempt to diagnose occult lung cancer 8.

Case report

A 31-year-old man with negative past medical history, smoker for the last 15 years (20 pack/year), had been physically extremely active, including diving. Dyspnea and productive cough started at the age of 31 years. Physical examination showed decreased breath sound with prolonged expiratory phase. Pulmonary function test parameters showed severe degree of the mixed type of ventilation insufficiency; diffusing capacity of the lung for carbon monoxide and transfer factor of the lung for carbon monoxide/ alveolar volume were significantly decreased (Table 1). Arterial blood gas analysis showed normal values (P_{O2}: 12.07 kPa, P_{CO2}: 5.05 kPa, pH: 7.40; HCO_{3}: 23.6 mmol/L; SaO_{2}: 96.9%).

Chest radiography and computed tomography (CT) scan showed bilateral diffuse massive pneumatoceles with minimal normal surrounding lung parenhyma (Figures 1a and b).

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right-sided pneumonia. *Klebsiella spp.*-*Enterobacter spp.* has been isolated from sputum. Lung function test results were similar to previous ones. After combined antibiotic therapy, the patient was dismissed fully recovered.

The patient came to see a doctor next time after two years, at the age of 36, when the signs and symptoms of pulmonary infection appeared again. Standard chest X-ray showed bronchopulmonary infiltrates in the basilar part of the left lung and the absence of the previously diagnosed bulla in the right lung – the status known as autobullectomy.

Control radiograph showed liquid formation in the bulla. CT scan showed large bulla in the left lung, 15 × 9 cm in diameter, with the liquid collection density of 9 Hounsfield unit (HU) (Figure 2).

After 5 weeks of antibiotic treatment, liquid collection disappeared.

Lung function tests showed moderate restriction pattern with decreased transfer factor and transfer coefficient (Lung transfer factor – TL 37%; transfer factor per unit alveolar volume – TL/VA 52%). His stable condition has been maintaining for the next five years up to the patient’s age of 41, when deterioration of his health started slowly. Hemoptysis appeared occasionally, together with dyspnea, purulent sputum production, and finger clubbing. Due to deterioration of pulmonary function with respiratory gases disturbance to severe degree of hypoxemia, he was hospitalized again at the age 42. This time, chest radiography and CT scan showed infiltration in the midle part of the right lung (Figure 3).

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### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Actual</th>
<th>Predicted</th>
<th>Percentages of predicted a/p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>3.59</td>
<td>5.49</td>
<td>65</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>1.8</td>
<td>4.38</td>
<td>41</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>50</td>
<td>81.8</td>
<td>61</td>
</tr>
<tr>
<td>DL,CO</td>
<td>3.72</td>
<td>11.7</td>
<td>32</td>
</tr>
<tr>
<td>TLC (L)</td>
<td>5.48</td>
<td>7.3</td>
<td>75</td>
</tr>
<tr>
<td>T,CO/VA mmol/min/kPa/L</td>
<td>0.75</td>
<td>2.1</td>
<td>34</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>34.4</td>
<td>25.7</td>
<td>134</td>
</tr>
<tr>
<td>RV (L)</td>
<td>1.89</td>
<td>1.79</td>
<td>106</td>
</tr>
</tbody>
</table>

The diagnosis of lung adenocarcinoma was confirmed by bronchoscopic biopsy. The patient died at the end stage of lung cancer after a 12-year follow-up of the previously diagnosed bullous lung diseases.

**Discussion**

We presented a 12-year history of the patient with gigantic bullous disease that is also known as vanishing lung syndrome (VLS), a primary bullous disease of the lung, or type I bullous disease, defined as giant bulla in one or both upper lobes, occupying at least one third of the hemithorax and compressing surrounding normal lung parenchyma 9. VLS in the presented patient was discovered by chance during an onset of respiratory infection. Clinical manifestations of bulla depend on the presentation of signs and symptoms of obstructive pulmonary disease. Usually, it is asymptomatic with periods of exacerbation with complications, and recovery, even when spontaneous rupture of the bulla with increase lung function occurs. It is shown that compressed lung parenchyma is functional and that surgical intervention would improve lung function and sustain progression of the disease. It would also decrease the risk of complications such as pneumothorax, infections of bulla, malignant alteration and hemothysis. While surgery in patients with isolated bulla should be recommended, bullous lung disease especially with complicated respiratory failure is extremely difficult to select for surgery. Although the presented patient was smoker at younger age, he had bullous lung disease with respiratory failure, so it was possible to discuss surgery 8, 10, 11.

Risk of cancer in patients with bullous disease is 36 times higher than in the normal lung parenchyma 10. The majority of these lung cancers are non-small-cell tumors, and this was the case with the reported patient, who had lung adenocarcinoma 4. The frequency of lung cancer associated with bullous emphysema has been estimated at 2–6% 12.

The potential carcinogenic mechanisms of bullous disease are still unrevealed. One of explanations is that carcinogens may inhibit antielastase enzymes, resulting in interalveolar septal destruction with consequent bulla formation. There is another opinion that constitutional or congenital factors may cause bullous disease and synchronously may also contribute to lung cancer predisposition 4. Related to this, the inner lining of a bulla may be more sensitive and susceptible to metaplastic alteration or disturbed aeration of bullae may allow easier carcinogens deposition. Another opinion suggests that the association of bullous lung disease and lung cancer is not only the consequence of shared tobacco smoking exposure, but, more probably, partial reflexion of a shared genetic predisposition to chronic smoking-induced inflammation 11.

Recent studies have put new light to the susceptibility to this disease. A genome-wide association study has revealed genetic variants in the nicotinic acetylcholine receptor (nAChR). The variants located on the chromosome 15q24/25 have been found to be associated with a risk for nicotine dependence, lung cancer, and chronic obstructive pulmonary disease (COPD) 12, 13. When it comes to emphysema, the 15q24/25 locus in nAChR was associated with both the presence and severity of the disease independently of total exposure to tobacco smoke (expressed in pack/years). The finding suggests that nAChR is causally involved in alveolar destruction process as a potentially common pathogenic mechanism in chronic obstructive pulmonary disease (COPD) and lung cancer. Even, if the increased air space is not managed by removal, as in our reported patient, air trapping with the bulla may contribute to generating of lung cancer 10.

The results of the studies on the association between COPD and lung cancer showed that disturbed lung function based on reduced forced expiratory volume in 1s (FEV1) is more important than the overall tobacco smoking exposure for lung cancer appearance 13, 14. In a chest CT screening study on 23 patients, the vast majority of subjects with lung cancer had either spirometric confirmation of COPD or radiological proof of variable intensity emphysema 15. Mortality studies show that 20–30% subjects with COPD die from lung cancer 16. Due to such a strong association COPD should be considered a major risk factor for lung cancer, greater than duration or tobacco smoke exposure 11. There is an opinion that lung function should be checked and followed up for assessing the risk of lung cancer just as it is reasonable to measure blood pressure in prediction of stroke, bone mineral density for eventual future bone fractures or body mass index as a risk factor in diabetes mellitus 14, 17, 18.

Measuring lung function should be very important for evaluation of lung cancer risk. This procedure of lung function testing for evaluation of lung cancer risk might be valuable in smoking cessation and targeted CT screening 15, 18.

Although it is suggested that airway obstruction and emphysema have been recognized as potential risk factors for development of lung cancer, the knowledge on clinical factors that contribute to lung cancer occurrence in subjects with COPD is still insufficient. A research showed that lung cancer can be expected in outpatients with COPD, more frequently in older ones with milder airflow obstruction (COPD stages I and II) and lower body mass index. Lung diffusion capacity of carbon monoxide less than 80% is associated with cancer diagnosis. The study showed squamous cell carcinoma as the most common histological type 19. Nowadays, clinicians knowing these factors make efforts in early detection of lung cancer and its treatment. The presence of emphysema affected disease outcome in patients with non-small cell lung cancer. Found common company of dominant emphysema and COPD in patients with lung cancer (70%) led to recommendation to consider these facts in prognostic studies on comorbidity 20.

Tobacco smoking is considered major risk factor for lung cancer. The presented patient was a heavy smoker. Chronic inflammation secondary to tobacco nicotine exposure is one of possible mechanisms between COPD and lung cancer. It holds up thinking that cancer develops at sites of fortified chronic inflammation 21. In smokers with bullous lung disease, tobacco smoke ingredients might have additional synergistic action with other factors that lead to cancerogenesis. Tobacco smoking influences macrophages and neutrophils that relax metalloproteases and reactive oxygen species. Such actions cause physiological modifications detected in COPD and/or lung cancer 22. Epithelial-mesenchymal transition, disturbed repair,
oxidative stress and cell proliferation probably take parts in the common elementary process, which binds the two diseases and causes extensive remodelling.

Smokers with genetic predisposition to excessive response to tobacco smoke contents have increased potential for lung tumor growth. Extensive airway remodelling may lead to epithelial-mesenchymal modification and malignant changes of respiratory epithelium. Still is unknown why some smokers develop pulmonary and not cardiovascular disease, and why some of those with pulmonary disease get COPD, some other cancer and some evolve both the diseases 23.

Literature data suggest chromosomal loci and several candidate genes associated with COPD and lung cancer such as 1q21-23 (C-reactive protein – CRP and interleukin – IL 6R), 4q22 (family – FAM 13A), 4q24 (glutathione S-transferase, C-terminal domain chonaining – GSTCD) and 4q31 (hedgehog interacting protein – HHIP and glucophorin A – GYP A) 24. Research is needed to explain genetic correlation between COPD and lung cancer.

Conclusion

In clinical practice, even asymptomatic smokers with pulmonary bullae should be carefully checked up annually. High-resolution chest CT to discover possible lung cancer is especially recommended.

REFERENCES


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