CASE REPORTS

UDC: 616.24-006-02-07
DOI: 10.2298/VSP150422077N

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

Plućna bula kao faktor rizika od karcinoma pluća

Ljudmila Nagorni-Obradović*†, Dragica Pešut*†, Dragana Marić*†, Ruža Stević*‡

***Faculty of Medicine, University of Belgrade, Belgrade, Serbia; †Teaching Hospital of Pulmonology, ‡Centre of Radiology and Magnetic Resonance, Clinical Center of Serbia, Belgrade, Serbia**

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.

Apstrakt

Uvod. Rezultati skorašnjih genetskih istraživanja ukazuju na moguću etiološku povezanost karcinoma pluća i plućne bule. **Prikaz bolesnika.** Bolesniku, starom 43 godine, pušaču, postavljena je dijagnoza gigantske plućne bule kada je imao 31 godinu. Praćen je pulmološki 12 godina, kada je na tom mestu otkriven karcinom pluća (adenokarcinom). U međuvremenu je lečen od ponavljanih respiratornih infekcija. **Zaključak.** Neophodan je aktivni pristup u praćenju bolesnika sa plućnom bulom zbog mogućeg nastanka karcinoma pluća kod tih bolesnika.

Ključne reči:
pluća, neoplazme; faktori rizika; bronhopneumonija; dijagnoza; tomografija, kompjuterizovana, rendgenska; bolest, progresija.

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 hystory, smoker for the last 15 years (20 pack/year), had been physicaly 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_aO_2: 12.07 kPa, P_aCO_2: 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).

Perfusion scan showed massive perfusion defects in the upper and lateral parts of both lungs. Concentration of α-1 antitripsin was 2.29 g/L, phenotipe Pi M_1. The patient did not accept a suggested surgical intervention.

The patient was symptom free for the next three years and then, at the age of 34, was hospitalized again due to

Correspondence to: Dragica Pešut, Faculty of Medicine, University of Belgrade, Clinical Centre of Serbia, Teaching Hospital of Pulmonology, Koste Todorovića 26, 11 000 Belgrade, Serbia. Phone: +381 11 366 3956. E-mail: dragica.pesut@mfub.bg.ac.rs

Table 1

Lung function test results on admission in the patient

Paremeter	Actual	Predicted	Percentages of predicted a/p
FVC (L)	3.59	5.49	65
FEV1 (L)	1.8	4.38	41
FEV1/FVC (%)	50	81.8	61
$D_{L,}CO$	3.72	11.7	32
TLC (L)	5.48	7.3	75
$T_{L,CO}$/VA mmol/min/kPa/L	0.75	2.1	34
RV/TLC	34.4	25.7	134
RV (L)	1.89	1.79	106

FVC − forced vital capacity; FEV_1 − forced expiratory volume in 1 s; $D_{L,}CO$ − diffusing capacity of the lung for carbon monoxide; TLC − total lung capacity; $T_{L,CO}$/VA − transfer factor of the lung for carbon monoxide/ alveolar volume; RV − residual volume; a – actual; p – predicted.

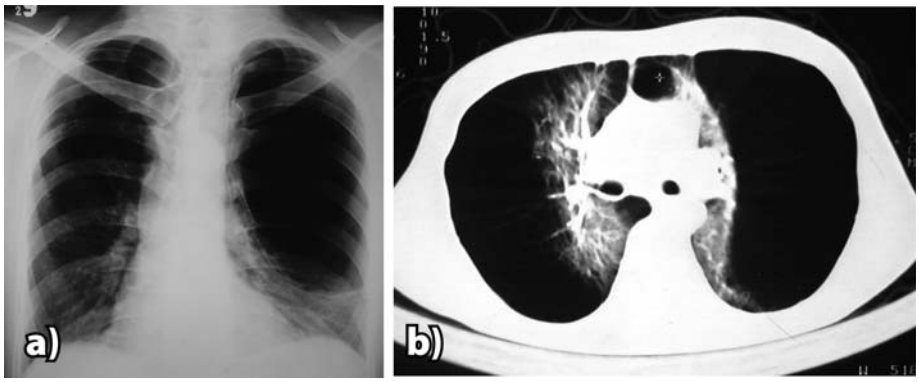

Fig. 1 − Bilateral diffuse massive pneumatoceles with minimal normal surrounding lung parenchyma shown by a) chest radiography, and b) computed tomography (CT) scan.

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 dissmised fully recovered.

The patient came to see a doctor next time after two years, at the age of 36, when the signs and symtoms of pulmonary infection appeared again. Standard chest x-ray showed bronchopulmonary infiltrates in the basal 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 disapeared.

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 stabile condition has been maintaining for the next five years up to the patient's age of 41, when deterioration of his health started slowely. Hemoptysis appeared occasionally, together with dyspnea, purulent sputum production, and finger clubbing. Due to deterioration of pulmonary function with respiratory gases disturbation 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).

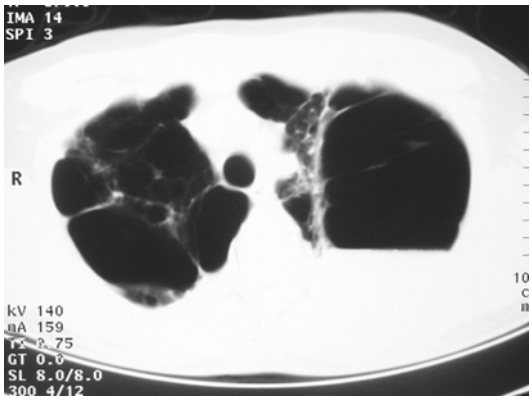

Fig. 2 – Computed tomography (CT) scan showed large bulla in the left lung, 15 × 9 cm in size, with the liquid collection density of 9 Hounsfeld unit (HU).

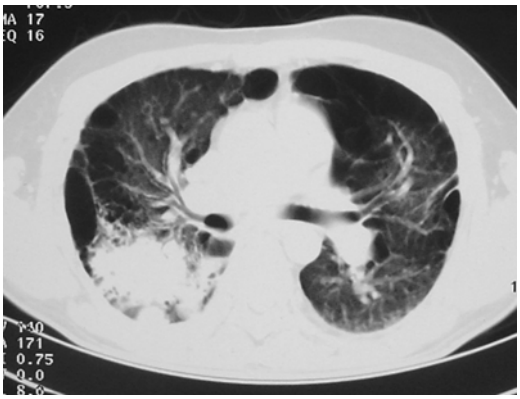

Fig. 3 – Chest radiography and computed tomography (CT) scan showed infiltration in the middle part of the right lung.

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 asympthomatic 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 alteracy and hemoptysis. 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 intervalveolar-septal destruction with consequent bulla formation. There is another opinion that constitutional or congenital factors may cause bullous disease and sinchronously 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 cncer, 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 (FEV_1) is more important than the overall tobacco smoking exposure for lung cancer appearence [11, 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 assesing 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 studes 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 ingrediens might have additional synergistic action with other factors that lead to cancerogenesis. Tobacco smoking influences macrophages and neutrophils that relax metalloproteinases 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 – GYPA) [24]. Research is needed to explaine genetic correlation between COPD and lung cancer.

Conslusion

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.

R E F E R E N C E S

1. *Deslauriers J, Leblanc P.* Bullous and Bleb Diseases, Emphysema of the Ling, and Lung Volume Reduction Operations. In: *Shields TW, Lociciro J, Ponn RB*, editors. General Thoracic Surgery. 5th ed. Philadelphia: Lippincott; 2000. p. 1001−38.
2. Global Initiative for Chronic Obstructive Lung Disease. NHLBI/WHO Workshop report. Available from: www.goldcopd.com [update 2011].
3. *Snider GL.* Chronic Bronchitis and Emphysema. Im: *Murray JF, Nadel JA*, editors. Textbook of Respiratory Medecine. Philadelphia, London, Toronto: WB Saunders; 1988. p. 1069−106.
4. *Ogawa D, Shiota Y, Marukawa M, Hiyama J, Mashiba H, Yunoki K*, et al. Lung cancer associated with pulmonary bulla. case report and review of literature. Respiration 1999; 66(6): 555−8.
5. *Venuta F, Rendina EA, Pescarmona EO, De GT, Vizza D, Flaishman I*, et al. Occult lung cancer in patients with bullous emphysema. Thorax 1997; 52(3): 289−90.
6. *Wilson DO, Weissfeld JL, Balkan A, Schragin JG, Fuhrman CR, Fisher SN,* et al. Association of radiographic emphysema and airflow obstruction with lung cancer. Am J Respir Crit Care Med 2008; 178(7): 738−44.
7. *Ben-Zaken CS, Paré PD, Man PS, Sin DD.* The growing burden of chronic obstructive pulmonary disease and lung cancer in women: Examining sex differences in cigarette smoke metabolism. Am J Respir Crit Care Med 2007; 176(2): 113−20.
8. *Zulueta JJ, Bloom SM, Rozansky MI, White AC.* Lung cancer in patients with bullous disease. Am J Respir Crit Care Med 1996; 154(2 Pt 1): 519−22.
9. *Sood N, Sood N.* A rare case of vanishing lung syndrome. Case Rep Pulmonol 2011; 2011: 957463.
10. *Stoloff IL, Kanofsky P, Magilner L.* The risk of lung cancer in males with bullous disease of the lung. Arch Environ Health 1971; 22(1): 163−7.
11. *Young RP, Hopkins RJ, Christmas T, Black PN, Metcalf P, Gamble GD.* COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. Eur Respir J 2009;4(2): 380−6.
12. *Watts MA, Klayton RJ, Munzel TL.* Bullous emphysema and carcinoma of the lung: Case report. Mil Med 1982; 147(4): 320−3.
13. *Lambrechts D, Buysschaert I, Zanen P, Coolen J, Lays N, Cuppens H,* et al. The 15q24/25 susceptibility variant for lung cancer and chronic obstructive pulmonary disease is associated with emphysema. A. J Respir Crit Care Med 2010; 181(5): 486−93.
14. *Turner MC, Chen Y, Krewski D, Calle EE, Thun MJ.* Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers. Am J Respir Crit Care Med 2007; 176(3): 285−90.
15. *Torres JP, Bastarrika G, Wisnivesky JP, Alcaide AB, Campo A, Seijo LM,* et al. Assessing the relationship between lung cancer risk and emphysema detected on low-dose CT of the chest. Chest 2007; 132(6): 1932−8.
16. *Lung Health Study Research Group.* Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med 2000; 343(26): 1902−9.
17. *Young RP, Hopkins RJ, Hay BA, Epton MJ, Black PN, Gamble GD.* Lung cancer gene associated with COPD: triple whammy or possible confounding effect. Eur Respir J 2008; 32(5): 1158−64.
18. *Bechtel JJ, Kelley WA, Coons TA, Klein GM, Slagel DD, Petty TL.* Lung cancer detection in patients with airflow obstruction identified in a primary care outpatient practice. Chest 2005; 127(4): 1140−5.
19. *Torres JP, Marín JM, Casanova C, Cote C, Carrizo S, Cordoba-Lanus E,* et al. Lung cancer in patients with chronic obstructive pulmonary disease: incidence and predicting factors. Am J Respir Crit Care Med 2011; 184(8): 913−9.
20. *Gullón JA, Suárez I, Medina A, Rubinos G, Fernández R, González I.* Role of emphysema and airway obstruction in prognosis of lung cancer. Lung Cancer 2011; 71(2): 182−5.
21. *Li Y, Swensen SJ, Karabekmez LG, Marks RS, Stoddard SM, Jiang R,* et al. Effect of emphysema on lung cancer risk in smokers: A computed tomography-based assessment. Cancer Rev Pres 2011; 4(1): 43−50.
22. *Adcock IM, Caramori G, Barnes PJ.* Chronic obstructive pulmonary disease and lung cancer: New molecular insights. Respiration 2011; 81(4): 265−84.
23. *Hardavella G, Spiro S.* Lung cancer in COPD. Eur Respir Monogr 2013; 59: 174−88.
24. *Young RP, Hopkins RJ, Gamble GD, Etzel C, El-Zein R, Crapo JD.* Genetic evidence linking lung cancer and COPD: A new perspective. Appl Clin Genet 2011; 4: 99−111.

Received on April 22, 2015.
Revised on July 30, 2015.
Accepted on August 3, 2015.
Online First April, 2016.