Case report

Developing lung cancer in COPD: Possible role of carrying Alpha-1 antitrypsin deficiency variants

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation and airway inflammation, with a prevalence of 10.1%. Among the many causes of COPD, Smoking is the leading and another big cause is (AATD α1-antitrypsin deficiency) an inherited disorder. Prevalence of COPD patients is 1.9%. World Health Organization (WHO) advice all COPD patients’ AATD rate to be screened at least once during their life.

The prevalence of AATD in the general population ranges from 1:2,000–5,000 in parts of Europe and from 1 to 5,000–10,000 in the United States and Canada.

Case 1: An 81-year-old male patient with COPD. In computed tomography (CT) of the thorax, mass in the right lower lobe and a nodule in the right upper lobe were detected. The biopsy from right bronchial entrance via fiberoptic bronchoscopy (FB) yielded squamous cell carcinoma (SCC). AAT level was 169 mg/dl (ref. range: 90–200 mg/dl). M/P lowell allele was detected in genetic analysis.

Case 2: A 45-year-old male patient with COPD. Conglomerated lymphadenomegaly in the para-tracheal area was detected in CT. The biopsy from mucosal infiltrates initiating from the entrance of the right upper lobe to the anterior segment revealed SCC. His AAT level was 190 mg/dl (ref. range: 90–200 mg/dl) and the genetic analysis demonstrated M/I mutation.

Case 3: A 64-year-old male COPD patient. In thorax CT, a 24 mm diameter parenchymal nodule in the left lower lobe was detected. Transthoracic fine needle aspiration biopsy from the left lung nodule showed SCC. His AAT level was 196 mg/dl (ref. range: 90–200 mg/dl) and M/P lowell allele was detected in the genetic analysis.

Discussion: AAT deficiency can cause early-onset of COPD, manifested with emphysema and chronic bronchitis. It has been suggested that AATD is associated with an increased risk of many types of cancer. Although the relationship between AATD or variant carriage and LC histopathology is not clear in the literature, it was detected as squamous cell carcinoma in our cases. We infer that unmeasurable lung damage is more prevalent in heterozygous patients and we believe that sharing our results may draw more attention in this regard.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation and airway inflammation, with a prevalence of 10.1% [1,2]. Among the many causes of COPD, Smoking is the leading and another big cause is (AATD α1-antitrypsin deficiency') an inherited disorder. Prevalence of COPD patients is 1.9% [3]. World Health Organization (WHO) advice all COPD patients’ AATD rate to be screened at least once during their life [4].

Alpha-1 antitrypsin (AAT) is a glycoprotein synthesized mainly by hepatocytes (80%) and in smaller amounts by other cells such as monocytes and macrophages. It is encoded in the locus of Protease inhibitor (Pi) which is in chromosome 14q321, and this gene is called SERPINA1. More than 125 genetic polymorphisms of this gene have been known [5]. The normal and most common allele is called PI * M and found in 85–90% of individuals. The most common missing alleles are PI * S and PI * Z and according to some studies, the incidence of these missing alleles have an incidence varies between 0.8% and 10% in world around [6,7]. The main function of AAT is to inhibit neutrophil elastase and other serine proteases. AAT provides more than 90% of the total antiprotease capacity of the organism and it has anti-inflammatory, immunomodulatory functions [8-10]. The prevalence of AATD in the general population ranges from 1:2,000–5,000 in parts of Europe and from 1 to 5,000–10,000 in the United States and Canada [11,12].

Lung cancer (LC) has a paramount role through comorbidities in COPD patients. In a control study AATD carriers have been reported to have a higher risk of compared to normal alleles [13]. It has been demonstrated in literature that malignancy is associated with AATD [13,14]. Only a limited number of studies have examined the LC risk of COPD patients with AATD or its variants. In one such research on LC patients, the authors reported 15% of the study population has both COPD and AATD [15].

We present three cases with COPD, diagnosed with AATD variant and concomitant comorbid LC. The aim of this report is to emphasize the probability of a higher LC development risk in COPD patients with AATD variant.

To detect AATD variants, the polymerase chain reaction (PCR) amplification of dried drop genomic DNA obtained from peripheral blood for gene mutation was used, followed by hybridization with allele-specific probes using Luminex xMAP Technology.

Case 1. An 81-year-old male patient with COPD who was a former smoker for 10 years and had 50 pack-year smoking history was admitted to the hospital. In computed tomography (CT) of the thorax, a 50 mm diameter mass in the right lower lobe and a 15 mm diameter nodule in the right upper lobe were detected (Fig. 1). The biopsy from right bronchial entrance via fiberoptic bronchoscopy (FB) yielded squamous cell carcinoma (SCC). AAT level was 169 mg/dL (ref. range: 90–200 mg/dL). M/P lowell allele was detected in genetic analysis. The patient died in the second month of the diagnosis due to respiratory failure.

Case 2. A 45-year-old male patient with COPD who was a current smoker with 58 pack-year was admitted to hospital. Conglomerated lymphadenomegaly in the paratracheal area was detected in CT. Emphysematous deteriorations were observed in both lungs (Fig. 2). Positron emission tomography/computed tomography (PET-CT) was reported as a centrally located very dense hypermetabolic mass (SUVmax: 11.09) distal to the right upper lobe bronchus. The biopsy from mucosal infiltrates initiating from the entrance of the right upper lobe to the anterior segment revealed SCC. His AAT level was 190 mg/ dL (ref. range: 90–200 mg/dL) and the genetic analysis demonstrated M/I mutation. Chemotherapy was given for stage IIIIB LC, and he died after one-year of the follow-up.

Case 3. A 64-year-old male COPD patient who had a smoking history of 30 pack-year was admitted to the hospital. In thorax CT, a 24 mm diameter parenchymal nodule in the left lower lobe was detected along with diffuse paraseptal emphysema in both upper lobes (Fig. 3). PET-CT demonstrated a very dense hypermetabolic lesion combined with the right infraclavicular lymph nodes. Hypermetabolic malignant nodul was observed in the posterobasal left lung. Transthoracic fine needle aspiration biopsy from the left lung nodule showed SCC and the patient staged as IIIIB. His AAT level was 196 mg/ dL (ref. range: 90–200 mg/dL) and M/P lowell allele was detected in the genetic analysis. He denied chemotherapy and died 9-month after diagnosis.

Fig. 1. In computed tomography (CT) of the thorax, a 50 mm diameter mass in the right lower lobe and a 15 mm diameter nodule in the right upper lobe were detected.
2. Discussion

COPD is one of the leading causes of morbidity and mortality in the worldwide [1]. AAT deficiency can cause early-onset of COPD, manifested with emphysema and chronic bronchitis. It has been suggested that AATD is associated with an increased risk of many types of cancer, especially the following: lung, liver, bladder and colorectal cancers, gallbladder adenocarcinoma and malignant lymphoma [16]. There are several carcinogenic mechanisms in LC development for AATD individuals. The main factor is an excess of neutrophil elastase, which can facilitate tissue damage and air trapping, leading to longer exposure to carcinogens in the alveoli [17]. By inhibiting apoptosis, it may cause tumor development through the tumor necrosis factor receptor signaling a pathway. Neutrophil elastase can activate matrix metalloproteinases, a group of enzymes involved in tumor invasion and metastasis. Some studies argue that high levels of neutrophil elastase, the main substrate of AAT, may have a role in lung carcinogenesis [18]. The role of AATD variants as risk factors in the development of LC has been confirmed by several studies supporting this argument [17]. Yang et al. have suggested that carrying AATD increases LC risk by 70–100% [13].

LC risk was observed to be significantly higher even surpassing that of patients with tobacco use. Besides smoking, another well-known risk factor for LC is COPD, which includes emphysema and chronic bronchitis. COPD not only increases the risk of LC for both smokers and non-smokers, but also shares common risk factors with LC [13]. A multi-center study including never-smokers and carriers of AATD without lung involvement concluded an increased risk of LC, especially in the histological type of adenocarcinoma [14]. Although the relationship between AATD or variant carriage and LC histopathology is not clear in the literature, it was detected as squamous cell carcinoma in our cases. The severity of the deficiency is related to the missing allele. AATD is associated with more than 95% of cases with the Pi * ZZ genotype and less frequently with other genotypes caused by Z, S, rare and null alleles [11]. It is known that COPD develops at varying rates in AATD homozygous and heterozygous carriers. Pi gene mutation in AATD directly increases the risk of LC [13]. The association between mutations involving the Z and S alleles and LC has been demonstrated. A rather low number of studies have shown an increased level of LC risk in homozygous and heterozygous AATDs. The present study has re-
ported three cases with normal serum AAT levels with heterozygous alleles, suggesting they may be overlooked if not tested. We infer that unmeasurable lung damage is more prevalent in heterozygous patients and we believe that sharing our results may draw more attention in this regard.

3. Conclusion

Since our country is a developing country, AATD is still not a widely researched subject for COPD patient. For this reason, we have limited number of patient at the first look. We believe that future studies will generate ideas. The cigarette exposure is an important risk factor for lung cancer. In our article, we would like to highlight whether there is a link between the risk of lung cancer in AATD patients with heterozygous mutations.

Subsequently, in all of these cases, heterozygous mutations may an important role in LC. Therefore, AATD should be controlled in patients with COPD.

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Declaration of competing interest

There are no conflicts of interest in connection with this paper.

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