e - ISSN - 2349 - 8005

INTERNATIONAL JOURNAL OF ADVANCES IN CASE REPORTS

Journal homepage: www.mcmed.us/journal/ijacr

ANTIPROTEASE DEFICIENCY AND RARE FORM OF CANCER: A CASE REPORT

Danielius Serapinas*

Mykolas Romeris University, Ateities 20, Vilnius, Lithuania.

Corresponding Author:- **Danielius Serapinas**
Email: dserapinas@gmail.com

Article Info

Received 15/09/2015
Revised 27/10/2015
Accepted 02/11/2015

Key words:
Protease, Cancer, health.

ABSTRACT

An increased incidence of deficiency of serum antiproteases has been reported in patients with chronic obstructive pulmonary disease but has not been well proven in association with other conditions. Currently taking place around the world debate on the role of serpin (serine protease inhibitor) in tumor genesis. Protease inhibitors such as alpha-1 antitrypsin were kept counteract tumor progression and metastasis, because of their ability to inhibit proteases. So is there any connection between inherited alpha-1 antitrypsin deficiency and Chondrosarcoma? Here is reported 47-year-old woman, that was admitted to the Oncology Department because of humerus Chondrosarcoma signs . The patient also had a history of chronic obstructive pulmonary disease. After a chest X-ray and consulting pulmonologist alpha-1 antitrypsin deficiency was suspected. Severe Alpha-1 antitrypsin deficiency (PIZZ homozygous genotype) was established. Alpha 1-antitrypsin deficiency may have facilitated the development of Chondrosarcoma. Due to the low incidence of such diseases, we assume that there is little chance of such rare disorders goes together in the same patient.

INTRODUCTION

Alpha-1 antitrypsin (AAT) deficiency is an autosomal-codominant genetic disorder that predisposes individuals to the development of liver and lung disease [1,2]. Alpha-1 antitrypsin deficiency is an under-recognized condition worldwide with only a minority of affected individuals detected, long diagnostic delays between initial symptoms and diagnosis, and evidence that patients may see many physicians with suggestive symptoms before an exact diagnosis is made [3,4].

The AAT protein is encoded by the protease inhibitor (PI) locus located on chromosome 14q32.1 [3]. Primary AAT function is to inhibit neutrophil elastase In severe deficiency, anti-elastase protection in the lung interstitium and alveolar space is markedly decreased to about 15–20% of normal levels, similar to the decrease in plasma levels The PI locus is highly polymorphic, and approximately 100 variants have been identified [1,3]. Normal serum levels (1- 2.5 g/l) of AAT are associated with the M allele [3]. Most of the pathology related to AAT deficiency is linked to the Z allele, and in clinical practice, 96 % of AAT deficiency patients have a ZZ genotype. The remaining 4% belongs mostly to SZ, MZ and other rare deficiency genotypes [4]. Recent guidelines from the World Health Organization and the American Thoracic Society/European Respiratory Society recommended screening programs suitable for the creation of AAT deficiency detection in patients with chronic obstructive pulmonary disease [1].

Worldwide debate takes place among scientists regarding the role of serpin (as serine protease inhibitors) in tumor genesis. Tumor progression, which is made up of tumor growth, invasion and metastasis may be boosted synthesized in cancer cells and / or host cells [2]. Protease inhibitors, which provide protection against the serine protease activity includes the AAT and some other serpin [2]. Protease inhibitors generally been considered to counteract tumor progression and metastasis, as their ability to inhibit the protease [2]. However in this case we are not sure whether ATT deficiency could promote the progression Chondrosarcoma.

Chondrosarcoma is a bone tumor of mesenchymal origin [3]. The aim of this report is to discuss all the possible clinical and pathophysiological relationship in patient with Chondrosarcoma and inherited AAT deficiency.

Case report

47-year-old non-smoking woman with signs of relapse of humerus Chondrosarcoma was admitted to the Department of Oncology, LUHS for radiation therapy. The patient complained of malaise, shortness of breath, coughing, and exertion. Her past medical history included surgery performed in 2004 Chondrosarcoma of the left proximal humerus. The patient was 15-year history of COPD treated with inhaled glucocorticoids and long-acting bronchial tubes. In a clinical trial Wheezy has been found in the chest X-ray and CT studies were performed. Chest CT identified a number of institutions both fibrous lung metastases without. Pulmonary emphysema with Bullae were founded in the largest bullae was 3 cm in diameter. Laboratory test showed 0.26 g / L of serum AAT concentration. It showed severe AAT deficiency (20% of normal range). AAT phenotype was evaluated in Isoelectric focusing, thus creating PIZZ phenotype. Spirometry showed third degree of bronchial obstruction: FEV1 - 30% (0,73l) FTC - 64% (1,80l), FEV1 / VC 0.3. Upper abdominal ultrasonography showed no abnormal changes in liver size was normal, smooth and homogeneous structure.

The patient was dismissed with AAT deficiency diagnosis. Also was recommended that appropriate genetic testing of family members. Specific treatment therapy for AAT can be recommended, but it was not indicated in this case. According to the recommendations made by the ERS / ATS, AAT drug treatment is not effective enough, if FEV1 is less than 50% [1].

DISCUSSIONS

Based on the examination of this case, we made the assumption that AAT deficiency can lead to a higher risk of development and progression Chondrosarcoma course. Even if there is no clear risk to development Chondrosarcoma , for individuals with homozygous AAT deficiency, several reports have shown a possible association with the other types of tumors [4, 5]. An increased risk of liver, bladder and bladder cancer, biliary, colon cancer, pancreatic carcinoma, breast cancer, malignant lymphoma, lung cancer and some other types have been found to be related to the inbalance of protease inhibitors [2 , 4].

The very first documented fact has been revealed that inherited AAT deficiency is a major risk factor for the development of liver cancer. Daily production of AAT is 34mg per kilogram of body weight, and about 70% of the human AAT is synthesized by hepatocytes and it is secreted into the circulating blood [1,2]. It is found in more than 75 allelic variants of the protease inhibitors locus, but the typical variations that lead to a certain lack of AAT is S and Z [1]. PIZZ AAT deficiency is a serious inherited condition that leads AAT plasma levels up to approximately 20% of the normal stems from the fact that the intracellular accumulation of secretion and obstruction, but not due to decreased AAT synthesis [6]. From Z AAT polymers in the endoplasmic reticulum of hepatocytes retention may cause liver damage due to hepatitis and liver cirrhosis for hepatocellular carcinoma [7].

Hereditary AAT deficiency also may be a risk factor for lung cancer, particularly squamous cell carcinoma, bronchoalveolar carcinoma, or [5]. Lung cancer is believed to be lower circulating protease inhibitors that can protect against attack neutrophil elastase [2] lungs result. Neutrophil elastase destroys elastin wall breathing terminal device and it has to consider among COPD and lung cancer path role [1]. We claim the initiation of Chondrosarcoma may be caused by AAT deficiency, which optionally is formed between proteases and their inhibitors imbalance as well.

After several reports of clinical trials, we have found a link between AAT deficiency and an increased risk of malignant lymphoma. Because of the potential role of AAT in view of the problems of development lymphoprolipheration hypothesis was an increased incidence of abnormal phenotypes Pi (Pi Pi MZ HS) of malignant lymphomas [8]. Anaplastic large cell lymphoma is non-Hodgkin lymphoma subtype, and some data indicate that the serpin A1 has invasion promoting the development of [9].

Our assumption is that the protease inhibitors and protease imbalance can lead to an increased number of neutrophil elastase. Serine protease or a neutrophil elastase prevents the host cells and it is the most destructive enzymes in the body. Kawabata and his colleagues reported that the destructive role raised neutrophil elastase may cause acute lung injury [11,12]. Elastase can degrade not only eliminate microorganisms or other organic molecules that have undergone phagocytosis by neutrophils [13,14], but it can also worsen the insoluble elastin and hydrolyze some of the other proteins, including collagens, fibronectins, proteoglycans and other extracellular matrix proteins [15-19]. Neutrophil elastase may also impair the growth factors involved in tumor genesis [4]. Total raised concentrations of neutrophil elastase can cause tissue damage and destruction beginning, thus promoting the development of cancer. Same as elastolytic destruction caused by protease in the lungs can lead to bone and cartilage tissues.

Thus chondrosarcoma is a cartilage cancer. Cartilage is composed of specialized cells called chondrocytes, which produce a large amount of extracellular matrix composed of collagen fibers, a lot of ground material which is rich in proteoglycan and elastin fibers [2]. Significant effects of metaloproteinases (MMP) for tumor invasion and metastasis has already been established [16].

Cartilage degradation can be initiated by an MMP, particularly MMP-13 [17]. The main type of cartilage is collagen type II collagen and it is degraded by MMP-13 (collagenase-3) [17]. MMPs can be activated by neutrophil elastase in 1 gus type matrix metalloproteinase [4]. In general, increased levels of MMP can cause damage to the cartilage [17] and cause malignant tumors. Thus alpha-1 antitrypsin deficiency, which can increase neutrophil elastase levels in the body gives rise to proteolytic activity of MMP [4]. The genesis of cancer at the molecular level in the nucleus of human cells, runs to the SOS system activity - when the DNA repair system is running. [4] These systems are intended to identify errors in DNA, preventing cell transformation and malignisation [18-20]. These changes can cause cell transformation and tumor occurrence. Another possible mechanism may be a process where neutrophil elastase lowers cell response to TNF and cause non-ceasing cell growth [4]. So Chondrosarcoma is multifactorial disease, that represents a number of possible triggers for the start of the tumor.

TNF-α - inflammatory cytokine is important in COPD pathogenesis [20, 21] and processes where AAT is involved [22]. In vitro studies have demonstrated that AAT inhibits TNF-α production [23]. However, no associations between serum TNF-α concentration and other parameters have been found in our study. It is observed that TNF-α levels may be elevated in the sputum, bronchial biopsies, and circulation of COPD patients [24-26]. Other investigators analyzing TNF-α level in COPD patients did not find any association with the severity of disease [7]. One possible explanation for this could be that these cytokines mainly act in peripheral lung tissues and differences in their levels could be detected in induced sputum but not always in systemic circulation. Thus sTNFR-1 is positively correlated with inflammatory markers – AAT and CRP. In addition, a positive correlation between sTNFR-1 and sTNFR-2 was documented. These soluble receptors, which inhibit the inflammatory effect of TNF-α, are expressed and released from many different cells, enabling even elevation of concentration in systemic circulation, where they can be detected [1]. Monocytes / macrophages are a significant component of inflammatory infiltrate in COPD [1, 27-28]. This observation provides evidence that a direct relationship exits between the accumulation of sCD14 and the reciprocal decrease in mCD14 expression. The biological function of sCD14 is not clear so far. An excess of sCD14 is shown to inhibit LPS binding to mCD14 and hence block cellular activation [29]. Recent findings support the hypothesis that a modulation of LPS-induced monocyte activation by AAT may be related to the AAT-induced modulation of CD14 levels [30-34].

These data show that AAT has immunomodulating capacity, and a rapid increase in AAT concentrations during various inflammatory and infectious conditions may enhance the magnitude of inflammatory cell responses to endotoxin and subsequently accelerate resolution of the inflammatory reaction [35-38]. However, associations are complex and understanding the interplay of various mediators will require appropriately designed further studies.

Based on our findings, we suggest that AAT deficiency may facilitate development of Chondrosarcoma. Both diseases are in very low frequency in general population. Frequency of Chondrosarcoma was 8 cases per 1 million people [19]. Therefore, AAT deficiency rate is generally 1: 5000 [20]. Because of this low incidence, we can assume that there is only a slight chance of these two rare diseases occurs together in the same patient.

ACKNOWLEDGEMENT: None

CONFLICT OF INTEREST:
The authors declare that they have no conflict of interest.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures performed in human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

REFERENCES

1. Yang P, Wentzlaff KA, Katzmann JA et al. (1999). Alpha 1-antitrypsin deficiency allele carriers among cancer patients. *Cancer Epidemiol Biomarkers Prev,* 8(5), 461-5.
2. Zelvyte I (2004). Academic Dissertation, Alpha 1-antitripsin, a role in cancer progression. Lund University, Malmö,
3. Berend KR, Toth AP, Harrelson JM et al. (1998). Association between ratio of matrix metalloproteinase-1 to tissue inhibitor of metalloproteinase-1 and local recurrence, metastasis, and survival in human chondrosarcoma. *J Bone Joint Surg Am,* 80(1), 11-7.
4. Sun Z, Yang P. A (2004). Role of imbalance between neutrophil elastase and alpha 1-antitrypsin in cancer development and progression. *Lancet Oncol,* 5(3), 182-90.
5. American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society statement, standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency (2003). *Am J Respir Crit Care Med, 168*(7), 818-900.
6. Parfrey H, Mahadeva R, Ravenhill NA et al. (2003). Targeting a surface cavity of alpha1-antitrypsin to prevent conformational disease. *J Biol Chem,* 278(35), 33060-6.

7. Eriksson SG, Carlson JA, Lindmark BE (1988). Serine proteinase inhibitors as acute phase reactants in liver disease. *Tokai J Exp Clin Med*, 13(6), 365-71.
8. Callea F, Massi G, De Wolf-Peeters C et al. (1982). Alpha-1-antitrypsin phenotypes in malignant lymphoma. *J Clin Pathol*, 35(11), 1213-5.
9. Duplantier MM, Lamant L, Sabourdy F et al. (2006). Serpin A1 is overexpressed in ALK+ anaplastic large cell lymphoma and its expression correlates with extranodal dissemination. *Leukemia*, 20(10), 1848-54.
10. Benkmann HG, Hanssen HP, Ovenbeck R, et al. (1987). Distribution of alpha-1-antitrypsin and haptoglobin phenotypes in bladder cancer patients. *Hum Hered*, 37(5), 290-3.
11. Needham M, Stockley RA (2004). Alpha 1-antitrypsin deficiency. 3, Clinical manifestations and natural history. *Thorax*, 59(5), 441-5.
12. Kawabata K, Hagio T, Matsuoka S (2002). The role of neutrophil elastase in acute lung injury. *Eur J Pharmacol*, 451(1), 1-10.
13. Weinrauch Y, Drujan D, Shapiro SD et al. (2002). Neutrophil elastase targets virulence factors of enterobacteria. *Nature*, 417(6884), 91-4.
14. Gronski TJ Jr, Martin RL, Kobayashi DK et al. (1997). Hydrolysis of a broad spectrum of extracellular matrix proteins by human macrophage elastase. *J Boil Chem*, 272(18), 12189-94.
15. Gabazza EC, Taguchi O, Yoshida M et al. (1995). Neutrophil activation and collagen metabolism in lung cancer. *Clin Chim Acta*, 236(1), 101-8.
16. Folgueras AR, Pendás AM, Sánchez LM et al. (2004). Matrix metalloproteinases in cancer, from new functions to improved inhibition strategies. *Int J Dev Biol*, 48(5-6), 411-24.
17. TAN Tzu-Wei, LAI Chih-Ho, HUANG Chun-Yiu et al. (2009). CTGF Enhances Migration and MMP-13 Up-Regulation Via αvβ3 Integrin, FAK, ERK, and NF-KB-Dependent Pathway in Human Chondrosarcoma Cells. *J Cell Bioch*, 107(2), 345-356.
18. Troll W, Meyn MS, Rossan TG (1977). Mechanisms of protease action in cancinogenesis. *Carcinogenesis*, 2, 301-12.
19. Hide G, Chondrosarcoma (2009). Available from URL, http, //emedicine. medscape. com/article/388869-overview.
20. Sitkauskiene B, Serapinas D, Blanco I et al. (2008). Screening for alpha1-antitrypsin deficiency in Lithuanian patients with COPD. *Respir Med*, 102(11), 1654-8.
21. Welle I, Bakke PS, Eide GE et al. (2001). Increased circulating levels of alpha1-antitrypsin and calprotectin are associated with reduced gas diffusion in the lungs. *Eur Respir J*, 17, 1105-11.
22. Stockley RA, Burnett D (1979). Alpha-1-antitrypsin and leukocyte elastase in infected and non-infected sputum. *Am Rev Respir Dis*, 120, 1081-6.
23. Owen CA, Campbell EJ (1999). Extra-cellular proteolysis, new paradigms for an old paradox. *J Lab Clin Med*, 134, 341-51.
24. Higashimoto Y, Yamagata Y, Taya S et al. (2008). Systemic inflammation in chronic obstructive pulmonary disease and asthma, similarities and differences. *Spirology*, 13, 128-133.
25. Meyer KC, Rosenthal NS, Soergel P et al. (1998). Neutrophils and low-grade inflammation in the seemingly normal aging human lung. *Mech Ageing Dev*, 104, 169-81.
26. Gan WQ, Man SF, Senthilselvan A et al. (2004). Association between chronic obstructive pulmonary disease and systemic inflammation, a systematic review and a meta-analysis. *Thorax*, 59, 574-80.
27. Silverman EK, Province MA, Rao DC et al. (1990). A family study of the variability of pulmonary function in alpha 1-antitrypsin deficiency. Quantitative phenotypes. *Am Rev Respir Dis*, 142, 1015-21.
28. Barnes PJ, Shapiro SD, Pauwels RA (2003). Chronic obstructive pulmonary disease, molecular and cellular mechanisms. *Eur Respir J*, 22, 672-88.
29. Sin DD, Man SF (2003). Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation*, 107, 1514-9.
30. Shaaban R, Kony S, Driss F et al. (2006). Change in C-reactive protein levels and FEV1 decline, a longitudinal population-based study. *Respir Med*, 100, 2112-20.
31. Kony S, Zureik M, Driss F et al. (2004). Association of bronchial hyperresponsiveness and lung function with C-reactive protein (CRP), a population based study. *Thorax*, 59, 892-6.
32. Gould JM, Weiser JN (2001). Expression of C-reactive protein in the human respiratory tract. *Infect Immun*, 69, 1747-54.
33. Van Eeden SF, Tan WC, Suwa T et al. (2001). Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants (PM10). *Am J Respir Crit Care Med*, 164, 826-30
34. Sin DD, Lacy P, York E et al. (2004). Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, 170, 760-5.
35. Lessiani G, Falco A, Franzone G et al. (2008). Prevalence of deep vein thrombosis in patients affected by exacerbation of mild to moderate COPD at stage I-II of GOLD classification. *Arch Med Sci*, 4, 62-5.

36. Janciauskiene SM, Nita IM, Stevens T (2007). Alpha1-antitrypsin, old dog, new tricks. Alpha1-antitrypsin exerts in vitro anti-inflammatory activity in human monocytes by elevating cAMP. *J Biol Chem*, 282, 8573-82.
37. Libert C, Van Molle W, Brouckaert P et al. (1996). Alpha1-Antitrypsin inhibits the lethal response to TNF in mice. *J Immunol*, 157(11), 5126-9.
38. Hacievliyagil SS, Gunen H, Mutlu LC et al (2006). Association between cytokines in induced sputum and severity of chronic obstructive pulmonary disease. *Respir Med*, 100, 846-54.