BIOLOGIJA. 2010. Vol. 56. No. 1–4. P. 74–77
DOI: 10.2478/v10054-010-0002-7

Inherited Alpha-1 antitrypsin deficiency and chondrosarcoma: a possible causal relationship

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Alpha 1-antitrypsin deficiency is a genetic risk factor for manifestation of COPD and chronic liver diseases. There is an ongoing worldwide discussion concerning the role of serpins (serine protease inhibitors) in tumour genesis. Protease inhibitors such as alpha 1-antitrypsin have generally been considered to counteract tumour progression and metastases because of their ability to inhibit proteases. In this case report, we analyze relationship between inherited alpha-1 antitrypsin deficiency and chondrosarcoma. A 47-year-old woman was admitted to the hospital with relapse signs of humerus chondrosarcoma. The patient had also a history of COPD. After chest X-ray and CT, alpha 1-antitrypsin deficiency was suspected. Inherited alpha-1 antitrypsin deficiency (PiZZ homozygous genotype) was confirmed. Alpha 1-antitrypsin deficiency might have facilitated the development of chondrosarcoma. Because of low incidence rate of such diseases, we presume that there is a slight chance for such rare disorders to manifest concurrently in the same patient.

Key words: alpha 1-antitrypsin deficiency, chondrosarcoma

Abbreviations: COPD – chronic obstructive pulmonary disease; serpins – serine protease inhibitors; CT – computed tomography.

INTRODUCTION

Severe hereditary deficiency of alpha 1-antitrypsin (AAT) is a genetic risk factor for manifestation of chronic obstructive pulmonary disease (COPD) and chronic liver diseases. AAT is a 52 kDa alpha-1-glycoprotein produced in the liver; it is responsible for protease inhibition. AAT deficiency is known to be related to an improperly diagnosed condition. Recent guidelines from both the World Health Organization and the American Thoracic Society / European Respiratory Society recommend the establishment of appropriate screening programs for the detection of AAT deficiency in patients with COPD. Detection of coexisting AAT deficiency in COPD patients should lead to the screening of family members, in order to facilitate appropriate management (including AAT replacement therapy in selected cases) and the specific counseling of such patients and their families [1].

Worldwide discussions take place among scientists concerning the role of serpins (as serine protease inhibitors) in tumour genesis. Tumour progression, which comprises tumour growth, invasion and metastases, can be promoted by proteases synthesized by cancer cells and / or host cells [2]. The protease inhibitors that provide protection against the activity of serine proteases include AAT and some other serpins [2]. Protease inhibitors have generally been considered to counteract tumour progression and metastases because of their ability to suppress the effect of proteases [2]. So, in this case, we are not sure whether ATT deficiency could have promoted the progression of chondrosarcoma. Chondrosarcoma is a bone tumour of mesenchymal origin. It is a type of highly malignant tumour with a potent capacity to invade locally and cause distant metastases [3].

The aim of this report is to discuss all possible clinical and pathophysiological relationships in a patient with chondrosarcoma and inherited AAT deficiency.

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CASE REPORT

A 47-year-old non-smoking woman with relapse signs of humerus chondrosarcoma was admitted to the Oncology Department of the Kaunas Medical University Hospital for radiation therapy. The patient complained of malaise, cough and shortness of breath during exercise. Her past medical history included operation performed in 2004 for chondrosarcoma of the proximal part of the left humerus. The patient had a 15-year-history of COPD treated with inhaled glucocorticosteroids and long acting bronchodilatators. During clinical examination, wheezes were detected and chest X-ray and CT examinations were done. Chest CT identified a few fibrous bodies in both lungs without metastases. Lung emphysema with bullae was established; the biggest bulla was 3 cm in diameter. Laboratory tests revealed 0.26 g/l AAT concentration in serum. It showed a severe AAT deficiency (20% of the normal level). The AAT genotype was evaluated, performing isoelectric focusing, thus establishing the PiZZ genotype. Spirometry showed the third degree of bronchial obstruction: FEV1 30% (0.73l), FVC 64% (1.80l), FEV1 / VC 0.3. Upper abdominal ultrasonography did not show any abnormal changes; the liver was of a normal size, smooth and of a homogeneous structure.

The patient was discharged with the diagnosis of AAT deficiency. Appropriate genetic testings for family members were recommended. No specific treatment with medication of AAT was indicated in this case because, according to the ERS / ATS recommendation, treatment with AAT medications is not sufficiently effective if FEV1 is less than 50% [1].

DISCUSSION

Relying on the results of examination of this case, we made a presumption that AAT deficiency could lead to a higher risk of chondrosarcoma development and progression. Even if there is no clear risk of developing chondrosarcoma in homozygous AAT-deficient individuals, several reports have demonstrated a possible association of this deficiency with other types of tumours [4, 5]. An increased risk of liver, bladder and gall bladder cancers, colorectal cancer, pancreatic carcinoma, breast cancer, malignant lymphoma, lung cancer and some other types have been found to be related to an imbalance between protease and its inhibitor [2, 4].

The very first documented fact has been that inherited AAT deficiency is a serious risk factor for developing liver cancer. Daily production of AAT is 34 mg per kg of body weight; about 70% of human AAT are synthesized by hepatocytes and secreted into the circulating blood [1, 2]. Over 75 allelic variants at the protease inhibitor locus have been identified, but the most common variants that lead to a deficiency of AAT are S and Z [1]. PiZZ AAT deficiency is a severe hereditary condition leading to AAT deficiency in blood because of the blockage of its secretion and intracellular accumulation but not because of reduced AAT synthesis [6]. The retention of Z-AAT polymers in the endoplasmic reticulum of hepatocytes can cause liver damage due to hepatitis and liver cirrhosis due to hepatocellular carcinoma [7].

Inherited AAT deficiency can also be a risk factor for lung cancer, especially squamous cell carcinoma or bronchoalveolar carcinoma [5]. Lung cancer is believed to be a result of reduced levels of circulating protease inhibitors unable to protect the lungs against neutrophil elastase attack [2]. Neutrophil elastase destroys the elastin walls, the terminal respiratory unit and has a role in the pathway between COPD and lung cancer risk [1]. We claim that chondrosarcoma initiation can be caused by AAT deficiency, which inevitably results in an imbalance between proteases and their inhibitors.

In a few clinical research reports we have found a correlation between AAT deficiency and an increased risk of malignant lymphoma. The hypothesis of a possible role of AAT in the development of lymphoprolipheration disorders was supported by an increased incidence of abnormal Pi phenotypes (Pi MZ, Pi SS) in malignant lymphomas [8]. Anaplastic large cell lymphoma is a subtype of non-Hodgkin's lymphoma, and some data suggest that serpin A1 has an invasion-promoting effect on its development [9].

The very first report about an elevated elastase activity in human bladder cancer cells was published in 1987. Pi Z alleles can be detected in patients with confirmed bladder cancer. Additionally, an association between a lowered normal AAT M allele frequency and bladder carcinoma was observed [10].

It is an essential question to answer: what can truly promote cancer genesis? Most of publications have reported that an imbalance between protease (neutrophil elastase) and their inhibitors (AAT) can cause cancer. But imbalance does not mean only an abnormal AAT concentration. Normal amounts of AAT in blood or an abnormal content of neutrophil elastase, or abnormal levels of both can also facilitate cancer progression [4].

Our hypothesis concerning the mechanisms of chondrosarcoma carcinogenesis is based on the deficiency of AAT which plays multiple biological roles in tumour genesis. AAT acts as an endogenous inhibitor of overexpressed proteases, especially of neutrophil elastases [11]. Our assumption is that the imbalance between proteases and their inhibitors can lead to an increased number of neutrophil elastases. Serine protease, or neutrophil elastase, protects host cells and is the most destructive enzyme in the body. Kawabata and colleagues have reported that the destructive role of

raised neutrophil elastase can cause an acute lung injury [12]. Elastase is able to degrade not only extraneous microorganisms or other organic molecules that have undergone phagocytosis by neutrophils [13], but it can also degrade insoluble elastin and hydrolyze some other proteins including collagens, fibronectins, proteoglycans and other extracellular matrix proteins [14, 15]. Neutrophil elastase can also degrade the growth factors that take part in tumour genesis [4]. Altogether, a raised concentration of neutrophil elastase can induce the onset of tissue damage and destruction, thus promoting cancer development. The same elastolytic destruction as induced by protease in lung can appear in bone and cartilage tissues. In our clinical case, the diagnosis of the patient was *Chondrosarcoma myxomatosum cysticum* as chest radiography revealed bullae formations in her lungs. Thus, it may have the same causal mechanism for cystic structure.

Chondrosarcoma is a cartilage cancer. Cartilage is composed of specialized cells, called chondrocytes, which produce large amounts of the extracellular matrix composed of collagen fibers, an abundant ground substance which is rich in proteoglycan and elastin fibers. Several classes of proteinases released by inflammatory or cancer cells might assist in the degradation of the extracellular matrix and can influence tumour growth, invasion and metastases [2]. A significant impact of matrix metalloproteinases (MMPs) in tumour invasion and metastases has already been established [16]. Cartilage degradation can be initiated by MMPs, especially MMP-13 [17]. The major type of collagen in cartilage is type II collagen; it is degraded by MMP-13 (collagenase-3) [17]. MMPs can be activated by neutrophil elastase through membrance-type 1 matrix metalloproteinase [4]. Generally, an increased level of MMPs can do damage to cartilage [17] and cause malignancy, or acquired alpha 1-antitrypsin deficiency which can increase neutrophil elastase level in the body, giving rise to proteolytic activity of MMPs [4].

Cancer genesis, at the molecular level of the nucleus of human cells, triggers the activity of the SOS system when the DNA repair system is out of order [4]. The role of this system is to fix DNA errors in order to prevent cell transformation and malignisation. New experimental data show that protease can hydrolyze protein repressors of the SOS system [18]. These changes can lead to transformation of cells and to the onset of tumour. The other possible mechanism might be the process when neutrophil elastase reduces cell response to TNF and causes a nonceasing cell growth [4]. Thus, chondrosarcoma is a multifactorial disease with various possible triggers for tumour initiation.

Relying on our findings, we presume that AAT deficiency might facilitate the development of chondrosarcoma. Withal, the incidence of these two diseases is very small. The incidence peak of chondrosarcoma in general population was 8 cases per 1 million [19]. Therefore, the frequency of AAT deficiency is about 1 : 5000 in European population [20]. Because of such a low incidence rate, we can suppose that there is only a slight chance for these two rare diseases to manifest themselves concomitantly in the same patient.

ACKNOWLEDGEMENT

The publication has been supported by the project VP1-3.1-ŠMM-05-K-01-022 "Strengthening the potential of the Lithuanian Biochemical Society in developing knowledge society".

Received 4 June 2010
Accepted 10 July 2010

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GALIMAS PRIEŽASTINIS PAVELDIMO ALFA-1 ANTITRIPSINO TRŪKUMO IR CHONDROSARKOMOS RYŠYS

Santrauka

Alfa 1-antitripsino trūkumas yra genetinis rizikos veiksnys, galintis nulemti lėtinę obstrukcinę plaučių ligą ir lėtines kepenų ligas. Pasaulyje diskutuojama dėl serpinų (serino proteazių slopiklių) poveikio navikų atsiradimui. Proteazių slopikliai, pavyzdžiui, alfa-1 antitripsinas, slopindami proteazes, veikia naviko progresavimą ir metastazavimą. Šiuo klinikiniu atveju analizuojame ryšį tarp paveldėto alfa-1 antitripsino trūkumo ir chondrosarkomos. Keturiasdešimt septynerių metų moteris buvo paguldyta į ligoninę dėl žastikaulio chondrosarkomos recidyvo. Pacientė daug metų serga ir lėtine obstrukcine plaučių liga. Atlikus krūtinės ląstos rentgenogramą ir kompiuterinę tomografiją buvo įtartas ir patvirtintas įgimtas alfa-1 antitripsino trūkumas (PiZZ homozigotinis genotipas), kuris galėjo lemti chondrosarkomos išsivystymą. Kadangi abi patologijos – alfa-1 antitripsino trūkumas ir chondrosarkoma – itin retos, yra labai nedidelė tikimybė, kad abi pasireikštų tam pačiam žmogui.

Raktažodžiai: alfa-1 antitripsino trūkumas, chondrosarkoma