Psychiatria Danubina, 2017; Vol. 29, Suppl. 4, pp S841–S844
Medicina Academica Mostariensia, 2017; Vol. 5, No. 1-2, pp 123-126 *Original paper*

TUMOR MARKER CA 125 IN THE DIAGNOSIS OF ACTIVE PULMONARY TUBERCULOSIS – A STUDY OF ADULTS IN MOSTAR, B&H

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received: 27.3.2017; revised: 4.7.2017; accepted: 15.11.2017

SUMMARY

Background: *Tumor marker CA 125 is found in normal mesothelial lung cells and normal bronchial epithelial cells. If destruction of these cells occurs due to inflammation or tumour, CA 125 will be released, and increased in the serum.*

Subjects and Methods: *From November 2008 to May 2009 a study analysing CA 125 levels in serum samples from patients who are hospitalized at the Pulmology Department of University Hospital Mostar. Standard laboratory tests, X-ray, sputum examination to BK, and tumour marker CA 125 were performed in all patients. Patients were divided into 5 groups. Comparing clinical and laboratory findings of patients and statistical processing of collected data, conclusions were drown about the role of tumor markers Ca 125 in the diagnosis of pulmonary tuberculosis.*

Results: *This analysis is performed on 220 patients, forty with pulmonary tuberculosis. Of the total number of patients included, there is 60% of the negative findings of tumor marker Ca 125 which is statistically significant ($P<0.05$). Further analysis of Ca 125 shows that there is 75% of positive findings in active pulmonary tuberculosis, which is a statistically significant difference ($P=0.002$). Within the group of patients with lung carcinoma, half of the patients showed positive finding of tumor marker CA 125. Statistical analysis showed that sensitivity of CA 125 was 75%, specificity was (68%) and positive predictive value was 12% in patients with active tuberculosis.*

Conclusions: *The result of this study showed that the increase in serum tumor marker CA 125 is present in active pulmonary tuberculosis as well as in patients with lung cancer.*

Key words: *tuberculosis, diagnosis - lung cancer – sensitivity - CA 125*

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INTRODUCTION

Exact and early diagnosis of tuberculosis is important, as untreated disease may be fatal in 5 years in more than half of cases (Crofton & Horne 2001). However, diagnosis of active tuberculosis is difficult to achieve. Presumptive diagnosis of tuberculosis is commonly based on the chest radiograph of upper lobe infiltrates with cavitations in patient with abnormal respiratory symptoms, and finding of acid fast bacilli (AFB) on microscopic examination of expectorated sputum or biopsy of lymphoid tissue. But, no radiographic finding in patients with tuberculosis is considered diagnostic. The presence of AFB discovered by direct microscopy in the patient's material is not sufficient criteria for diagnosis of tuberculosis, as the possibility that changes are caused by Mycobacterium other then tuberculosis exists. Skin testing with PPD is of limited value in the diagnosis of active tuberculosis because of its low sensitivity and specificity.

Definitive diagnosis is done by isolation and identification of Mycobacterium tuberculosis (MT) from a diagnostic specimen, usually from sputum in a patient with a productive cough. However, species of mycobacterium grows slowly, and 4 to 8 weeks are required before detecting the growth. Another new method (using of liquid media for isolation and speciation by nucleic acid probes or high pressure liquid chromatography of mycolic acids) decreased the time for bacteriologic confirmation to 2 to 3 weeks (Peroš & Pavlović 2002). Direct diagnosis of tuberculosis could be made by polymerase chain reaction. Test is fast, findings can be obtained in one day, but not specific nor sensitive enough as conventional methods for diagnosis of tuberculosis (Grosset & Mouton 1995). Serological tests such as enzyme-linked immunosorbent assay and radioimmunoassay have not yet found their place in the diagnosis of tuberculosis due to low sensitivity and specificity. Tumour marker CA 125 appears in the epithelial cells of ovarian cancer. As a tumour marker, it showed low sensitivity and specificity in many studies (Moss et al. 2005). Carlson and colleagues reported that the increased values of serum CA 125 is present in women with ovarian cancer 78% (Carlos et al. 1994). Matsuako found increased value of CA 125 in extrapulmonal tuberculosis (Matsuako et al. 1987). The rationale of this phenomenon is that CA 125 is found in normal mesothelial lung cells and normal bronchial

epithelial cells. If destruction of these cells occurs due to inflammation or tumour, CA 125 will be released, and increased in the serum (Simsek et al. 1997).

Yilmaz and colleagues (Yilmaz et al. 2001) found that CA 125 in serum had 97.5% sensitivity and 100% specificity in discrimination active from inactive pulmonary tuberculosis. Ozsahin and colleagues noted 63% sensitivity and 59 % specificity of CA 125 in differentiating acute from inactive pulmonary tuberculosis (Ozsahin et al. 2008). Diez and colleagues (Diez et al. 1991) reported that the serum concentration of CA 125 was higher in patients with benign pulmonary diseases, including pulmonary tuberculosis, compared to healthy population. Alimagham and colleagues (Alimagham et al. 2006) described elevated levels of CA 125 in two patients with miliary tuberculosis. The increase in CA 125 levels was also observed in abdominal tuberculosis by other authors (Younssian et al. 2006, Thakur et al. 2001, Best et al. 1998). As a conclusion, there is no simple, accurate, rapid and cheap method for diagnosis of tuberculosis. Some authors recommend CA 125 tumour marker as a rapid serologic method with high sensitivity and specificity (Yilmaz et al. 2001), while others reported the opposite (Ozsahim et al. 2008). The information available on the tumour markers value in diagnosis of tuberculosis is insufficient. The aim of this study was to establish value of tumour marker CA 125 in patients with active pulmonary tuberculosis.

PATIENTS AND METHODS

Two hundred twenty patients were studied between November 2008 and May 2009. A hundred and sixty three patients were male and 57 female. The mean age of the entire group was 65 (range 18-89 years). Patients were hospitalized at the Pulmology Department, University Hospital Mostar.

Standard laboratory tests, X-ray, sputum examination to BK, and tumour marker CA 125 were performed in all patients. Serum analysis was made in the laboratory of University Hospital Mostar using ARCHITECTi2000 system. Method for determination of tumour marker CA 125 was performed in two steps in order to find the presence of specific antigens in human serum or plasma using CMIA (chemoluminescent micro particle immunoassay). The sample was added to the reagent (Abbott Laboratories Diagnostics Division, Abbott Park, IL, USA) containing paramagnetic micro-particles for the CA 125 tumour marker 75µL. Chemoluminescent reactions were measured as relative light units (RLUs). ARCHITECT optical system detects the connection between a particular antigen in the sample and the RLUs. The results of CA 125 were defined in U/mL units, and positive values were > 35 U/mL.

Patients were divided into 5 groups.

The first group consisted of 40 patients with active pulmonary tuberculosis, second group made 30 patients with inactive pulmonary tuberculosis, third group made 63 patients with lung tumours, fourth group consisted of 30 patients with chronic obstructive pulmonary disease (COPD) and fifth group consisted of 57 patients with other lung diseases including pneumonia and sarcoidosis.

Diagnosis of active and inactive pulmonary tuberculosis was made by analysis of sputum for BK (3 times) and lung X-ray. Active pulmonary tuberculosis was diagnosed on the basis of positive sputum culture for BK. Inactive pulmonary tuberculosis was diagnosed on the basis of history of previous episode of tuberculosis with documentation of positive culture at the time of diagnosis, and three sputum negative cultures for BK. Lung tumours were diagnosed by analysis of biopsy samples taken by bronchoscopy. Chronic obstructive pulmonary disease (COPD) was diagnosed by spirometry findings. Pneumonia was diagnosed by physical and radiographic findings. Diagnosis of sarcoidosis is based on the biopsy through a fiberoptic bronchoscope in the context of clinical picture, laboratory findings and lung x-ray images.

The statistical analysis included 220 patients of which 74% were men and 27% were women. The average age of patients in this study is 65 years. Equally represented are the patients diagnosed with COPD and inactive pulmonary tuberculosis. There were 40 patients diagnosed with active pulmonary tuberculosis in this period. In that period, it is clear that statistically the most represented patients were those, who were diagnosed with lung cancer and patients diagnosed with other diseases.

Cultures for BK were performed in Loewenstein-Jensen media.

The patients with incomplete medical documentation were excluded from study.

During the study, all ethical principles prescribed by international, European and national codes of ethics, have been followed and respected (Puri et al. 2009). Obtained results were used only for the purposes of this research and not for any other purpose. The patients remained anonymous.

In accordance with the results of Kolmogorov–Smirnov test on normal distribution of data, the appropriate statistical test was chosen for this study (Kruskal-Wallis test). For comparison of nominal and ordinary data χ^2 test was used. Fisher's exact test and Mann-Whitney U test were used when the lack of expected frequencies occurred. The level of statistical significance was defined as $P < 0.05$.

Test of sensitivity and specificity, and positive and negative predictive value were used for a statistical analysis of the validity of the diagnostic test.

Table 1. Frequency of tumor marker Ca 125 in relation to the diagnosis

Diagnosis	Tumor marker CA 125 (%)		test	
	Positive	Negative	χ^2	*p*
Active pulmonalry tuberculosis	30 (75)	10 (25)	10.000	0.002
Inactive pulmonary tuberculosis	5 (16.7)	25 (83.3)	13.333	<0.050
Lung tumours	34 (54)	29 (46)	0.397	0.529
COPD*	4 (13.3)	26 (86.7)	16.133	<0.050
Other lung diseasis	16 (28.1)	41 (71.9)	10.965	0.001

* COPD - Chronic obstructive pulmonary disease

Table 2. Sensitivy and specificity of thr test in the patients with active tuberculosis

Tumor marker	Sensitivity of the test (%)	Specificity of the test(%)	PPV* (%)	NPV** (%)
CA 125	0.75 (75)	0.681 (68)	0.126 (12)	0.978 (97)
CA 19-9	0.035 (3)	0.904 (90)	0.021 (2)	0.941 (94)
CEA	0.096 (9)	0.790 (79)	0.026 (2)	0.937 (93)

* PPV – Positive predictive value; ** NPV – Negative predictive value

RESULTS

Of the total number of patients included in this survey, there is 60% of the negative findings of tumor marker CA 125, and 40% of positive findings, which is statistically significant (χ^2=8.018; df=1; P<0.05). Further analysis of tumor marker CA 125 shows that there is 75% of positive findings in active pulmonary tuberculosis, which was a statistically significant difference (χ^2 test=10,000; df=1; P=0.002) (Table 1). Within the group of patients with lung carcinoma, half of the patients showed positive findings of tumor marker CA 125. Statistically we have significantly higher negative results in inactive pulmonary tuberculosis and COPD and within the group of patients with other lung diseases. Observing the tumor marker CA 19-9, we discovered that statistically there are more negative findings in all experimental groups. Statistical analysis of tumor markers CEA shows that there is a higher prevalence of negative findings in all experimental groups. Statistical analysis showed that sensitivity of CA 125 was 75%, specificity was (68%) and positive predictive value was 12% in patients with active tuberculosis (Table 2).

DISCUSSION

Moss, Hollingworth, Reynolds found elevated levels of CA 125 in 50% in first stage of ovarian epithelial cancers. The sensitivity of CA 125 for ovarian cancer in female population was 88.6 %, but with specificity of only 72%. As marker lacks sensitivity and specificity to detect ovarian cancer at an early stage it was not considered as a screening test in diagnosis of ovarian cancer. CA 125 was also raised in tumours of lungs, breasts, bowel, pancreas, and in some other non-malignant conditions such as endometriosis, liver cirrhosis and heart failure.

There is no specific fast laboratory test that would indicate active pulmonary tuberculosis, and lung X-ray findings are often confusing. Only isolation and identification of M. tuberculosis from a diagnostic specimen could diagnose active tuberculosis. However, result is available in 4-6 weeks, and during that period it could be important to know serum levels of tumour marker CA 125, which could imply whether the patient has active tuberculosis. According to Yilmaz and colleagues CA 125 had high sensitivity and specificity in active pulmonary tuberculosis. Besides, Ozsahin and colleagues suggest that CA 125 is of great importance in differentiating active from inactive tuberculosis.

The result of this study showed that the increase in serum tumour marker CA 125 was present in active pulmonary tuberculosis and in patients with lung cancer. The available literature mostly observed values of tumour marker CA 125 in women with proven abdominal tuberculosis.

But, the results of this study did not showed high sensitivity and specificity. It was concluded that CA 125 could not be useful in screening or diagnosis of tuberculosis, and that introducing of one additional non-specific diagnostic test would confuse both patients and physicians.

Acknowledgements: None.

Conflict of interest : None to declare.

Contribution of individual authors:

All autors contributed to the conception of the article.
Marijana Mikačić and Mario Šimović collected data;
M. Vasilj and D. Bevanda analysed te collected data;
Ivan vasilj and K. Galić Contributede to literatire research and monitoring the patientes.

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