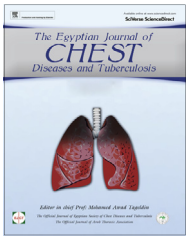
Egyptian Journal of Chest Diseases and Tuberculosis (2013) 62, 419–424

The Egyptian Society of Chest Diseases and Tuberculosis

Egyptian Journal of Chest Diseases and Tuberculosis

www.elsevier.com/locate/ejcdt
www.sciencedirect.com



ORIGINAL ARTICLE

# Role of cancer antigen 125 in active pulmonary tuberculosis

**Azza Farag Said** [a,*], **Bahaa Ibrahim Mohamed** [a], **Esmat El-Sharkawy** [b], **Miral Al-Sherif** [a]

[a] *Department of Chest Diseases, Faculty of Medicine, Minia University, Egypt*
[b] *Department of Clinical Pathology, Faculty of Medicine, Minia University, Egypt*

Received 13 July 2013; accepted 31 July 2013
Available online 23 August 2013

**KEYWORDS**

Cancer antigen 125;
Pulmonary tuberculosis;
Prognostic marker

**Abstract** *Background:* Conventional TB diagnosis continues to rely on smear microscopy, culture and chest radiography. Other non-conventional approaches include detection of immunological response and the search for biochemical markers. Cancer antigen 125 (Ca-125) was evaluated mainly in patients with extra pulmonary TB.

*Objective:* This study was designed to detect the role of Ca-125 in differentiating pulmonary tuberculosis from other pulmonary infections. Also to determine the value of Ca-125 was an indicator of response to anti-tuberculous drugs.

*Design:* Eighty patients were included in the study, 27 with active pulmonary TB and 33 with other pulmonary infections. Twenty healthy volunteers were used as a control group. Measurement of serum Ca-125 was performed once in all groups, it was re-assayed after 4 months of anti-tuberculous drugs among patients with active pulmonary TB.

*Results:* There was a significant increase of Ca-125 among patients with active pulmonary TB than the other groups, which decrease significantly after anti-tuberculous drugs. The sensitivity and specificity of Ca-125 were found to be 81.4% and 95%, respectively, at a 34.6 U/ml cut-off point.

*Conclusion:* Ca-125 can be a useful marker in differentiating pulmonary TB from other pulmonary infections and in assessment the response to anti-tuberculoussis drugs.



## Introduction

Tuberculosis represents an important health problem worldwide that was declared by World Health Organization (WHO) to be global emergency [1]. The World Health Organization estimates that each year more than 8 million new cases of tuberculosis occur and approximately 3 million persons die from the disease. Ninety-five percent of tuberculosis cases occur in developing countries [2].

* Corresponding author. Tel.: +20 0862355846.
E-mail address: azza20022@yahoo.com (A.F. Said).

☆ Peer review under responsibility of The Egyptian Society of Chest Diseases and Tuberculosis.

ELSEVIER Production and hosting by Elsevier

0422-7638 © 2013 The Egyptian Society of Chest Diseases and Tuberculosis. Production and hosting by Elsevier B.V.
Open access under CC BY-NC-ND license. http://dx.doi.org/10.1016/j.ejcdt.2013.07.016

It is estimated that 12 million patients are co infected with HIV and *Mycobacterium tuberculosis*, with the majority living in sub-Saharan Africa and Southeast Asia [3].

TB currently holds the seventh place in the global ranking of causes of death. Unless intensive efforts are made, it is likely to maintain that position through to 2020 [4].

Pulmonary TB, the most important type of TB from the public health point of view, can be diagnosed by its symptoms, chest radiography, sputum smear microscopy, and by cultivation of *M. tuberculosis* [5].

However, in some cases of pulmonary TB, acid-fast bacilli stains in sputum samples may be negative or respiratory specimens may not be available, and other methods have to be used to establish the diagnosis of TB.

Recent advances in the field of molecular biology have provided new tools for the rapid diagnosis of TB by molecular methods. However, the high cost of most of these techniques, and their requirement for sophisticated equipment or highly skilled personnel have precluded their implementation on a routine basis, especially in low-income countries [6].

Apart from microbiological molecular diagnostic tests, different biochemical parameters have been proposed as helpful tools for this purpose, including various markers of cellular activity, acute phase reactants and enzymes [7–11]. The tumor marker Cancer antigen 125 has been proposed as a useful diagnostic tool for tuberculosis [12].

Cancer antigen 125 or carbohydrate antigen 125 is a high molecular weight glycoprotein (200 KDa) which was identified on the surface of the ovarian carcinoma cell line OVCA 433 by Bast et al. in 1981 [13].

Ca 125 is most consistently elevated in epithelial ovarian cancer, but can be expressed in a number of gynecologic (endometrial, fallopian tube) and non-gynecologic (pancreatic, breast, colon and lung) cancers [14].

High levels of Ca-125 have been reported in patients with pulmonary and extra-pulmonary tuberculosis, including pleural, peritoneal, pelvic, miliary, and intraabdominal disease [15–19].

In pulmonary TB, it was claimed that raised levels of Ca 125 can greatly increase the likelihood of tuberculosis activity [20]. The diagnostic value of Ca-125 to help differentiate pulmonary tuberculosis from other pulmonary infections has been poorly studied [15–17].

## Aim of the work

The aim of this study was to detect:

1. The role of Ca-125 in differentiating active pulmonary tuberculosis from other pulmonary infections.
2. The value of Ca-125 as an indicator of response to antituberculous drugs among patients with active pulmonary tuberculosis.

## Subjects and methods

This study was performed at Minia Chest hospital and Minia University hospital from November 2011 to December 2012. This study was approved by the ethics committee of Faculty of Medicine, Minia University and a written consent was obtained from patients and controls. Eighty subjects participated in this study and were divided into the following groups:

*Group (A):* Included (27) patients with active pulmonary tuberculosis (14 males/13 females, mean age 36.5 years with range of 15–70). Active pulmonary TB was diagnosed based on clinical, radiological and bacteriological findings [21]. This group had a clinical symptoms of active pulmonary TB in the form of cough (subacute in 17 patients and chronic in 10 patients), hemoptysis (6 patients), fever (22 patients), loss of appetite (20 patients), weight loss (17 patients), night sweats and malaise (24 patients). Also, some patients had dyspnea (18 patients).

Radio-logically, this group had lung parenchymal abnormalities in the form of patchy shadows and cavitations. Patients were classified according to the National Tuberculosis Association of the USA [22] based on radiological extent of TB into (20) patients with moderate advanced and (7) patients with a far advanced lesions on chest X-ray. Bacteriologically, all of these groups had a sputum smear positive for acid-fast bacilli (AFB). Acid-fast bacilli stains were performed according to the Ziehl–Neelsen method. None had a previous history of pulmonary or extra-pulmonary TB.

All patients in this group received anti-tuberculous drugs in the form of (2 months of rifampicin, isoniazide, pyrazinamide and ethambutol followed by 4 months of rifampicin and isoniazide). After 2 months of treatment, sputum smears were repeated and conversion into sputum smear negative occurred in all patients.

*Group (B):* Included (33) patients with other pulmonary infections who had a history of cough and expectoration, pulmonary infiltrate ± fever. They were divided into two subgroups: group (B1) included (17) patients with community acquired pneumonia (CAP) (male/female: 11/6, mean age 42.1 years with range of 19–57) and group (B2) who were (16) patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) (male/female: 11/5, mean age 55.4 years with range of 43–65).

All group B patients had negative sputum smear for acid fast bacilli.

*Control group, group (C):* Comprised (20) healthy individuals (male/female: 11/9, mean age 34.8 years and range 19–57). They had no history of TB or other diseases and their chest X-rays were normal.

Patients with liver cirrhosis, ascites, renal failure, heart failure (left sided heart failure), those with known malignancy anywhere, patients with benign gynecological lesions as pelvic inflammatory disease (PID) or malignant gynecological tumors, pregnant, and menstruating females were excluded. It is reported that Ca 125 increases in these conditions [23].

All the three groups were subjected to history taking, general and local chest examination. Blood sampling for routine investigations (complete blood count, ESR for group A) and measurement of serum levels of Ca-125 were performed. Five ml of venous blood was drawn from each subject. Blood samples were left to clot for 15–20 min at 37 °C, then centrifuged at 3000 rpm for 20 min. Expressed serum was frozen at -40 °C till the time of Ca-125 assay.

Serum levels of Ca-125 were measured using VIDAS Ca 125 II (Biomérieux, France), which is an automated

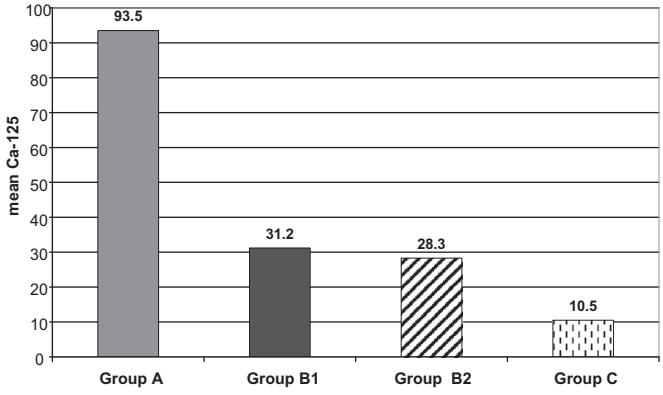



**Figure 1** Mean serum Ca 125 among the studied groups.

**Table 1** Pre and post treatment Ca 125 among patients with active pulmonary TB.

| | No. of cases | Serum Ca-125 | | *P* |
|---|---|---|---|---|
| | | Range | Mean ± SD | |
| Before treatment | 27 | 10.6–825 | 93.5 ± 158.9 | 0.001 |
| After 4 months of anti-TB drugs | 23 | 4–100 | 22.8 ± 25.6 | |

quantitative test on mini VIDAS instruments, for the measurement of OC125 antigenic determinants in human serum using Enzyme Linked Fluorescent Assay (ELFA). The results were automatically calculated by the instruments and the concentrations were expressed in U/ml.

Another assessment of serum Ca-125 was detected among group (A) only after 4 months of anti-tuberculous drugs.

### Statistical analysis

Data were analyzed statistically by SPSS software version 14. Qualitative data were expressed as number and percentage whereas quantitative data were summarized as mean ± standard deviation (SD). Student's *t*-test was used when comparing the means of quantitative data. Correlations between data were analyzed using Spearman correlation test. For all analyses, statistical significance was defined as $P$ values $\leqslant 0.05$.

### Results

Fig. 1 shows mean serum Ca 125 levels among the studied groups. It was found that mean Ca 125 levels were significantly higher among group A (93.5 ± 138.9 U/ml) compared to healthy controls (10.5 ± 7.3, $P = 0.004$) and other comparable groups (B1 = 31.2 ± 34.2, B2 = 28.3 ± 19.9, $P = 0.03$). On the other hand there was no significant difference between the values of Ca 125 among group B1 vs. B2 ($P = 0.7$).

Ca 125 levels were re-assayed after 4 months of anti-tuberculous drugs among group A. Twenty-three patients out of 27 could be reassayed and the other 4 failed to show for follow up. All the 23 patients were sputum smear negative for acid fast bacilli after 4 months of anti-tuberculous drugs. Table 1 shows pre and post anti-tuberculous drug levels of Ca 125 among group A. Ca 125 was significantly lower after treatment than before (22.8 ± 25.6 vs. 93.5 ± 158.9, $P = 0.001$).

**Table 2** Correlation co-efficient (*r*) between Ca 125 and radiological extent in patients with active pulmonary TB.

| Radiological extent | No. of cases | *r*-value | *P* |
|---|---|---|---|
| Moderate advanced | 20 | 0.56 | 0.003 |
| Far advanced | 7 | | |

There was a significant positive correlation between Ca 125 and radiological extent among group A ($r = 0.56$, $P = 0.003$) (Table 2).

For a value of Ca 125 in the diagnosis of active pulmonary TB, the sensitivity, specificity, positive, negative predictive values and accuracy of Ca 125 were found to be 81.4%, 95%, 95.6%, 79.2% and 87.2%, respectively, among group (A) at a Ca 125 $\geqslant$ 34.6 U/ml cut-off value. A ROC curve based on these data was constructed as shown in Fig. 2, AUC = 0.95 ± 0.02, 95%CI = 0.91–1.008, $P = 0.001$.

### Discussion

Although serum tumor markers were introduced in clinical use as biochemicals for monitoring response to therapy and detecting early relapse in malignancies, it has been observed that increased levels of these tumor markers can also be detected in benign conditions.

It was reported that serum Ca-125 levels were also higher than normal in patients with pulmonary and extra-pulmonary tuberculosis and that serum Ca-125 level may be a useful marker for discriminating between patients with active tuberculosis and those with inactive disease [9,20,26].

The results of this study had shown that serum Ca 125 level was significantly higher in patients with active pulmonary TB than both of healthy controls and patients with other pulmonary infections.

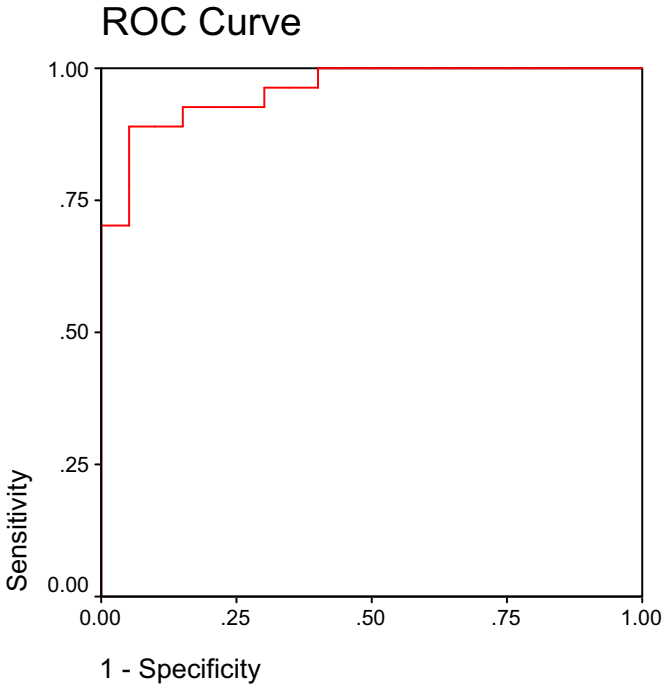



**Figure 2** Roc curve of Ca 125 among patients with active pulmonary.

Other studies have confirmed high serum Ca 125 levels in tuberculosis, mainly in extra pulmonary locations with abdominal involvement [19,20,24,25]. In Yilmaz et al. study [20], the mean Ca-125 level in patients with active pulmonary tuberculosis was (109.7 ± 86.9 U/ml), while it was (118.46 ± 248.41 U/ml) in Ozsahin et al. study [26] which are to some extent close to the value in the present study (93.5 ± 138.9 U/ml). On the other hand, Kim et al. study [30] showed a lower mean value of Ca 125 in patients with active pulmonary TB (54.5 ± 22.4) than in our study. This may be due to the difference in ways of the diagnosis of tuberculous patients. They depend on sputum culture while in this research; we depended on sputum smear-probably with a higher bacillary load than culture.

Ronay et al. [27] determined that Ca-125 was immunohistochemically localized and sharply demarcated around tuberculous granuloma in two patients with peritoneal tuberculosis. They concluded that a possible explanation for this finding was the inflammatory mesothelial cell proliferation which was the source for secretion of Ca 125 in patients with TB.

Another study [28] demonstrated that epitheloid and giant cells in both pleural effusion and ascites were stained with antibodies to Ca-125 in a patient with pleural and peritoneal tuberculosis.

Our results showed that Ca 125 was significantly lower in patients with CAP and those with AECOPD than in the pulmonary TB group. While Ozsahin et al. [26] found that the mean Ca-125 values of other comparable groups (CAP, AECOPD, pleural –pulmonary malignancy and others), were not statistically different from the mean value of patients with pulmonary tuberculosis ($P > 0.05$). This may be due to the difference in the severity of the other comparable groups in the two studies as regards the causative organism and the degree of inflammation.

It was found that there was a highly significant decrease of serum Ca-125 after 4 months of anti-tuberculous drugs than pretreatment level (22.8 ± 25.6 vs. 93.5 ± 158.9, $P = 0.001$).

In Yilmaz et al. study [20], measurements of serum Ca-125 were performed before treatment, then at the second, fourth, sixth months of anti-tuberculous drugs and at the third year following end of treatment. After 2 months of anti-tuberculous drugs, serum Ca-125 decreased significantly than before treatment (38.4 ± 30.5 vs. 109.7 ± 86.9 at pretreatment level). After 4 months of anti-tuberculous drugs, Ca-125 declined to 16.4 ± 13.2 U/ml.

In Fortún et al. study [12], Ca-125 levels were redetermined in 10 patients out of 35 patients with pulmonary tuberculosis after 2 to 4 months of anti-tuberculous drugs. The mean Ca-125 decreased significantly after anti-tuberculous therapy (104.9 ± 136.1 vs. 59.5 ± 88.5 U/ml).

In the present study, it was found that 20 patients (74%) of active pulmonary tuberculosis had a moderate advanced lesion on chest X-ray and 7 patients (26%) had a far advanced lesion. No patients had a minimal lesion on chest X-ray. Ca-125 was higher among patients with far advanced lesions than moderate advanced (80.7 ± 48 vs. 50.8 ± 49.5), respectively. Therefore, we can take Ca 125 as one of the parameters in the assessment of severity of TB. In addition, there was a significant positive correlation between Ca 125 and radiological extent ($r = 0.56$, $P = 0.003$). These results are in agreement with those reported by Kanagarajan et al. [29], who found that levels of Ca-125 being highest in cavitary pulmonary TB and in miliary TB. Kim et al. [30] also found that Ca-125 levels appeared to be highest in patients with cavitary rather than nodular type and this may reflect the level or extent of the infection.

In the present study, there was an insignificant correlation of age and sex to Ca 125 among all of the studied patients and

healthy controls. It was reported that Ca 125 was higher in premenopausal women than post-menopausal ones [31] while Fortún et al. [12] found that there was no significant correlation between Ca 125 and gender. In our study, there was also an insignificant correlation of ESR to Ca 125 among patients with active pulmonary TB.

At a serum Ca 125 of $\geqslant$34.6 U/ml as a cut-off value, it had sensitivity, specificity, positive and negative predictive values and diagnostic accuracy of 81.4%, 95%, 95.6%, 79.2% and 87.2%, respectively, among patients with active pulmonary TB. Fortún et al. [12] used a cut-off value of Ca-125 for TB diagnosis of 32.5 IU/ml, with sensitivity, specificity, positive predictive value and negative predictive value of 68.6%, 77.8%, 66.7% and 79%, respectively.

For estimation of the activity of TB, Yilmaz et al. [20] found a sensitivity and specificity of Ca 125 to be 97.5% and 100%, respectively at a 31 U/ml cut-off point.

In conclusion, the present study shows that serum Ca 125 levels in patients with active pulmonary tuberculosis are significantly higher than those observed in patients with other causes of pulmonary infections.

Ca 125 measurement may be recommended if pulmonary tuberculosis is suspected clinically and radio logically, acid fast bacilli stain of respiratory samples is negative, patients had a dry cough (with no sputum specimens available) or in children in whom the diagnosis of TB is difficult.

Ca-125 has a high sensitivity and specificity in the estimation of active pulmonary tuberculosis. So, if Ca-125 level is $<$ 34.6 U/ml in a suspected pulmonary tuberculosis case, one should prompt a search for alternate diagnosis than TB. It is definitely useful in the monitoring of therapeutic responses to anti-tuberculoussis drugs, predicting the prognosis and spotting those patients who are not going to respond early to anti-tuberculous drugs for whom 2nd line of anti-tuberculous drugs or the new line of treatment is started early.

## Conflict of interest

None declared.

## References


[1] World Health Organization. Global tuberculosis control: surveillance, planning, and financing. WHO report Geneva 2004; WHO/HTM/TB: 331.

[2] World Health Organization. Groups at Risk: WHO Report on the Tuberculosis Epidemic 1996. World Health Organization, Geneva, Switzerland.

[3] P.F. Barnes, D.L. Lakey, W.J. Burman, Tuberculosis in patients with HIV infection, Infect. Dis. Clin. North Am. 16 (2002) 107–126.

[4] C. Dye, S. Scheele, P. Dolin, V. Pathania, M.C. Raviglione, Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country, JAMA 282 (1999) 677–686.

[5] E.D. Chan, L. Heifets, M.D. Iseman, Immunologic diagnosis of tuberculosis: a review, Tuber Lung Dis. 80 (2000) 131–140.

[6] J. Foulds, R. O'Brien, New tools for the diagnosis of tuberculosis: the perspective of developing countries, Int. J. Tuberc. Lung Dis. 2 (1998) 778–783.

[7] F. Ameglio, D. Giannarelli, P. Cordiali-Fei, et al, Use of discriminant analysis to assess disease activity in pulmonary tuberculosis with a panel of specific and nonspecific serum markers, Am. J. Clin. Pathol. 101 (6) (1994) 719–725.

[8] M. Hosp, A.M. Elliott, J.G. Raynes, et al, Neopterin, beta 2-microglobulin, and acute phase proteins in HIV-1-seropositive and -seronegative Zambian patients with tuberculosis, Lung 175 (4) (1997) 265–275.

[9] Y. Aoki, O. Katoh, Y. Nakanishi, et al, A comparison study of IFN gamma, ADA, and CA125 as the diagnostic parameters in tuberculous pleuritis, Respir. Med. 88 (2) (1994) 139–143.

[10] R.A. Taha, T.C. Kotsimbos, Y.L. Song, et al, IFN-gamma and IL-12 are increased in active compared with inactive tuberculosis, Am. J. Respir. Crit. Care Med. 155 (3) (1997) 1135–1139.

[11] A. Verbon, N. Juffermans, S.J. Van Deventer, et al, Serum concentrations of cytokines in patients with active tuberculosis (TB) and after treatment, Clin. Exp. Immunol. 115 (1) (1999) 110–113.

[12] J. Fortún, P. Martín-Dávila, R. Méndez, A. Martínez, F. Norman, J. Rubi, E. Pallares, E. Gómez-Mampaso, S. Moreno, Ca-125: a useful marker to distinguish pulmonary tuberculosis from other pulmonary infections, The Open Respir. Med. J. 3 (2009) 123–127.

[13] R.C. Bast, M. Feeney, H. Lazarus, L.M. Nadler, R.B. Colvin, R.C. Knapp, Reactivity of a monoclonal antibody with human ovarian carcinoma, J. Clin. Invest 68 (5) (1981) 1331–1337.

[14] R.C. Bast, F.J. Xu, Y.H. Yu, S. Barnhill, Z. Zhang, G.B. Mills, CA 125: the past and the future, Int. J. Biol. Markers 13 (4) (1998) 179–187.

[15] T. Yoshimura, H. Okamura, Peritoneal tuberculosis with elevated serum CA 125 levels: a case report, Gynecol. Oncol. 28 (3) (1987) 342–344.

[16] S.A. Candocia, G.Y. Locker, Elevated serum CA 125 secondary to tuberculous peritonitis, Cancer 72 (6) (1993) 2016–2018.

[17] H. Simsek, M.C. Savas, A. Kadayifci, et al, Elevated serum CA 125 concentration in patients with tuberculous peritonitis: a case control study, Am. J. Gastroenterol. 92 (7) (1997) 1174–1176.

[18] N.F. de Paz, H.B. Fernandez, P.R. Simon, et al, Pelvic-peritoneal tuberculosis simulating ovarian carcinoma: report of three cases with elevation of the CA 125, Am. J. Gastroenterol. 91 (8) (1996) 1660–1661.

[19] G.A. Belletti, A.E. Millán, A. López, et al, Pelvic tumor, elevated CA 125 level and tuberculosis, Medicina (B Aires) 65 (2) (2005) 181–182.

[20] A. Yilmaz, F. Ece, B. Bayramgürler, E. Akkaya, R. Baran, The value of Ca 125 in the evaluation of tuberculosis activity, Respir. Med. 95 (8) (2001) 666–669.

[21] American Thoracic Society and Centre for Disease Control and Prevention (ATS/CDC). Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med 2000; 161: 1376–1395.

[22] National Tuberculosis Association of the USA, Diagnostic Standards and Classification of Tuberculosis, National Tuberculosis Association, New York, 1961.

[23] P. Buamah, Benign conditions associated with raised serum CA-125 concentration, J. Surg. Oncol. 75 (4) (2000) 264–265.

[24] A. Imai, T. Itoh, K. Niwa, T. Tamaya, Elevated CA125 serum levels in a patient with tuberculous peritonitis, Arch. Gynecol. Obstet. 248 (3) (1991) 157–159.

[25] A.B. Younossian, T. Rochat, L. Favre, J.P. Janssens, Ascites and highly elevated CA-125 levels in a case of peritoneal tuberculosis, Scand J. Infect. Dis. 38 (3) (2006) 216–218.

[26] S.L. Ozsahin, B. Turgut, N. Nur, O. Dogan, T. Erselcan, S. Berk, Validity of the CA-125 level in the differential diagnosis of pulmonary tuberculosis, Jpn. J. Infect. Dis 61 (2008) 68–69.

[27] G. Ronay, W. Jager, A.H. Tulusan, Immunohistochemical and serologic detection of Ca-125 in patients with peritoneal tuberculosis and ascites, Geburtshilfe Frauenheilkd 49 (1) (1989) 61–63.

[28] T. Hirose, S. Ohta, I. Sato, et al, Tuberculous pleuro-peritonitis showing increased levels of CA125, Nihon Kyobu Shikkan Gakkai Zasshi 35 (2) (1997) 196–200.
[29] K. Kanagarajan, J. Williams, V. Rupanagadi, M. Jalliard, G. Gandy, K. Gupta, P. Krishman, Is CA-125 a reliable serum marker for diagnosis of tuberculosis?, Chest 128 (2005) 141S
[30] S.Y. Kim, Yoonki Hong, Chang-Min Choi, Yeon-Mok OH, Sang Do Lee, Dong Soon Kim, Tae Sun Shim, Elevated serum CA-125 levels in patients with non-tuberculous mycobacterial lung disease, Respirology 15 (2010) 357–360.
[31] V.R. Zurawski, H. Oryeseter, A. Anderson, E. Jellum, Elevated serum CA 125 level prior to diagnosis of ovarian neoplasia: relevance for early detection of ovarian cancer, Int. J. Cancer 42 (1987) 677–680.