

Value of Ca 125 for diagnosis of pleural endometriosis in women with recurrent pneumothorax

P.Bagan ^{1 2}, MD, Pascal Berna ¹, MD, Jalal Assouad ¹, MD, Vincent Hupertan ², MD, PhD, Françoise Le Pimpec Barthes ¹, MD, and Marc Riquet ¹, MD.

1: Department of Thoracic Surgery.

Georges Pompidou European Hospital, Paris V University, Paris, France.

2: Department of Thoracic, Vascular Surgery and Urology. Clinic of surgery.

Victor Dupouy Hospital, Argenteuil, France

Address reprint request to Dr Riquet, service de Chirurgie Thoracique, Hôpital Européen

Georges Pompidou, 20-40 rue Leblanc, 75908 Paris, France

e-mail : marc.riquet@hop.egp.ap-hop-paris.fr

Tel: 00 33 1 56 09 34 50

Fax: 00 33 1 56 09 33 80

Short title: Diagnosis of thoracic endometriosis with CA125

ABSTRACT

Question of the study: Thorax is the most frequent extrapelvic location of endometriosis.

Thoracic endometriosis is probably responsible for the high rate of recurrent pneumothoraces in women. The goal of this prospective study was to assess the value of Ca125 measurement in the detection of endometriosis in order to further enable early and adequate treatment of catamenial pneumothorax.

Patients and Methods: From January 2004 to March 2006, 31 women, of mean age 32 years, underwent pneumothorax surgery. The control group was a group of 17 men of mean age 27 years, who underwent video-thoracoscopic pleural abrasion. The serum Ca 125 was measured each time around the menstrual period in women and before surgery in men.

Results : Videothoracoscopy diagnosed endometriosis in 29 % of women. The Ca125 concentration was significantly higher in women with endometriosis compared with disease-free women (76.1 U/ml versus 16 U/ml; $p < 0.0001$). The mean value in male was similar to that observed in disease-free women.

Answer to the question : Frequency of thoracic endometriosis related pneumothorax averages one third of women presenting with recurrent pneumothorax. Early detection can be achieved with serum Ca125 measurement, and may be helpful in the indication of videothoracoscopic surgery.

Key-words : Catamenial pneumothorax, CA 125, Thoracic endometriosis,.

TEXT

Introduction

Catamenial pneumothorax (CP) is an entity of recurring spontaneous pneumothorax in women during their reproductive years. It has been associated with thoracic endometriosis (TE), but its physiologic mechanism remains unclear. Traditional surgical pleurodesis is associated with a high rate of recurrence. Recently, Korom and associates [1] outlined the frequent lack of recognition of TE. The average number of recurrences before definitive diagnosis and treatment was 5.1 ± 6.0 (several reports listed more than 30 recurrences before treatment [2-4]). Actually, when TE is investigated in women within reproductive age with a spontaneous pneumothorax, even when the pneumothorax occurs out of the menstrual period, the rate of TE averages 25-30 % [5,6].

Tsunezuka and coll.[7] observed in cases of CP that immunohistochemical staining of endometrial cells on partial resection of the diaphragm showed antibodies to Ca125. The authors observed that serum Ca125 level which was very high before operation decreased to normal range after diaphragmatic resection. In a recent report, Kafali and coll. managed to successfully diagnose pelvic endometriosis by measurement of Ca125 level during menstruation [8]. Similarly, we intend to detect endometriosis in women with recurrent pneumothorax. Thus, the goal of this prospective study was to evaluate the serum Ca 125 level in the diagnosis of thoracic endometriosis in women within reproductive age presenting recurrent spontaneous pneumothorax and to hence enable adequate surgical and hormonal treatment.

Material and Methods

Patients:

From January 2004 to March 2006, 31 consecutive women referred at our institution for the surgery of primary spontaneous pneumothorax were included in the study. The mean age was 32 years (19-51). Investigation of gynaecological history was performed each time before surgery. Indications of surgery were recurrent pneumothorax (two or more episodes) n=21, persistent air leakage n=8, spontaneous hemopneumothorax n=1, postoperative recurrence n=1. A control group was chosen in order to avoid the possible perturbations of Ca 125 level caused by pleural effusion [9]. The control group was a group of 17 men with primary spontaneous recurrent pneumothorax who underwent video-thoracoscopic pleural abrasion during the beginning of the study period. The mean age in the control group was 27 years [16-56].

All patients gave informed consent and the study was approved by local ethics committees. The Ca 125 was prospectively measured once in all women around the menstrual period (ranged 2 days before to 2 days after) when the concentration reaches its highest value. The Ca 125 was measured before surgery in men. In female patients with a pneumothorax occurring outside the menstrual period, the Ca 125 was measured at the beginning of the next cycle in our outpatient clinic. The Ca 125 level was considered as normal when inferior to 35 U/ml (Hospital laboratory reference).

All patients underwent video-thoracoscopy. Blebs or bullae resection with stapler was performed systematically. Diaphragmatic surface was examined in the women. Diaphragmatic biopsies were performed each time defects and nodules were observed. In these cases, we applied our technique performed since 1990 [10]: the treatment of diaphragmatic defects consisted in insertion of a polyglactin mesh (Vicryl; Ethicon, Inc, Sommerville, NJ) to cover the tendinous part of the diaphragm. The mesh were held in place by endostaples.

Statistical analysis:

Statistical analysis were performed with SPSS 14 software (SPSS, Inc., Chicago, IL). All measurements are presented as mean \pm SD. Mean serum Ca125 concentrations were compared using a two-sample *t*-test for between-group comparisons and a paired *t*-test for within-group comparisons. A *p* value <0.05 was considered statistically significant. Optimum cutoff points to achieve maximum use as predictive test for diagnosis of thoracic endometriosis were calculated and receiver operating characteristics (ROC) curves were obtained using software.

Results

Clinical examination revealed that pneumothorax occurred during menses in 3 women with history of pelvic endometriosis and in 1 woman with personal history of idiopathic infertility and pleural abrasion after five recurrences. Pneumothorax occurred out of menses in two women with an history of pelvic endometriosis.

Videothoroscopic exploration and biopsies diagnosed thoracic endometriosis in 9 women. Endometrial glands or chorionic cells were observed on the diaphragm in 8 patients and on both diaphragmatic and parietal pleural surfaces in one patient. Pathologic examination of the lung resection revealed blebs in 16 patients, sarcoidosis in one and lymphangiomyomatosis in one. Surgical pleurodesis (pleural abrasion *n* = 29, pleurectomy *n*= 2) was performed in all patients.

The mean Ca125 concentration of the entire population was 27.4 \pm 32.1 U/ml. The mean level in the study group was higher than in the control group but not significantly (33.4 \pm 38.2 U/ml versus 16.4 \pm 9.7 U/ml; *p*=0.08). The Ca125 concentration was significantly higher in women with thoracic endometriosis compared with disease-free women (76.1 \pm 49.2 U/ml versus 16 \pm 8.1 U/ml; *p*< 0.0001)(Figure 1). Figure 2 shows the ROC plots for Ca 125 measurement. The area under the curve was 0,994. Optimum cutoff point to achieve

diagnosis of thoracic endometriosis was 39 U/ml with no false positive case and two false negative cases.

Discussion

The prevalence of endometriosis can be assumed to be around 10% among women of reproductive age [11]. Catamenial pneumothorax is the most frequent presentation of thoracic endometriosis (TE), syndrome described by Joseph et al [12]. The other TE presentations are catamenial haemothorax, pleural effusion and catamenial haemoptysis. Thoracic endometriosis is considered as a rare condition. Cases of catamenial pneumothorax are currently published as case reports considered as very rare entities [13]. Catamenial pneumothorax represents 29% (n= 9/31) of spontaneous pneumothorax in women. The rate we observed is in agreement with rates recently published in reports prospectively studying the prevalence of TE. This rate ranges from 25 to 33% [5,6]. The mean delay between first pneumothorax and diagnosis of TE is 2.4 years [1].

In two third of cases (n=6/9 in our population), women had history of sterility or pelvic disease. Thoracic endometriosis is perhaps underestimated because of the systematic gynecological examination lack. In one case of postoperative recurrence that we observed, endometriosis was suspected neither by the gynaecologist nor the thoracic surgeon or the pneumologist. The underestimated catamenial pneumothorax frequency may be one of the causes explaining the higher rate of recurrences in women. The most significant factor which may predispose to recurrence is gender. Females are likely to experience more recurrences than tall men [14, 15,16].

Association between endometriosis and elevated serum CA125 levels has long been known. The CA 125 antigen is expressed in amnion, in derivatives of fetal celomic epithelia and in many adult tissues (endometrium, endocervix, pleura, peritoneum and pericardium) [9].

Several authors have studied CA125 concentrations during different phases of the menstrual cycle and found clearly elevated CA125 concentrations during the premenstrual late secretory phase and during menstruation itself [11]. Recently, Kafali and coll. have conducted a study comparing normal women and patients with endometriosis, they observed a significant exaggerated serum Ca 125 elevation in patients with endometriosis during menstruation ($p < 0.001$) [8]. Fedele and coll.[17] have observed that patients with advanced stages of pelvic endometriosis according to the American Fertility Society classification [18] had serum Ca 125 levels significantly higher than the disease-free women. Mean Ca125 level in the control group of men with pneumothorax was significantly inferior to the level observed in women with TE. The sensitivity of serum Ca 125 measurement in the diagnosis of endometriosis recurrence was 14.8%, the specificity was 100%. Otherwise, Ca 125 is nonspecifically increased in any process that irritates the mesothelial cells. Most frequent pathologies which increased this marker are liver cirrhosis, heart failure, serosal effusions, pancreatic and gynecological processes [9]. The assessment of serum Ca125 level may be useful in the early diagnosis of TE in women within reproductive age presenting a primary spontaneous pneumothorax without gynaecological orientation and without clinical signs of malignant and nonmalignant conditions that injure mesothelial cells.

In summary, we suggest to include Ca125 measurement in the management of pneumothorax in women. Its elevation is a good indicator of thoracic endometriosis as is the gynaecological disease history. This biological marker may favour indication of videothoracoscopy and hormonal therapy at an early stage in the prevention of catamenial pneumothorax recurrences and it should be evaluated prospectively in a larger scale study.

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Fig.1 Comparison of CA 125 level according to diaphragmatic and pleural pathological examination in women ($p < 0.0001$).



Figure 2: ROC curve for CA 125 measurement.

