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Elevation of CA 19-9 and Chromogranin A, in Addition to CA 125, Are Detectable in Benign Tumors in Leiomyomas and Endometriosis

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As the best-known tumor marker for ovarian carcinoma, CA 125 has also been commonly used to monitor patients with common benign gynecologic diseases such as endometriosis and leiomyoma. Both of these benign tumors are known to be at risk of developing into cancer. During the screening of an asymptomatic population with multiple tumor markers, including alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), prostate-specific antigen (PSA), CA 125, CA 19-9, CA 15-3, chromogranin A (CgA), and squamous cell carcinoma antigen (SCC), we have detected elevated tumor markers in 142 individuals; 19 of them were diagnosed with endometriosis or leiomyoma or both. In addition to the detection of elevation of CA 125 in these benign tumors, elevated CA 19-9 or CgA was also found in these patients with endometriosis or leiomyoma. Many patients only had elevated CA 19-9 or CgA; the elevation of CA 125 was not detected. It appears that instead of monitoring only CA 125, as is traditionally done, multiple tumor markers, including CA 19-9, CgA, and CA 125, should be measured simultaneously in women with clinical disorders associated with the ovary or uterus in order to detect gynecologic benign tumors and in order to prevent further development of cancer. J. Clin. Lab. Anal. 21:193–196, 2007.

Key words: leiomyoma; endometriosis; benign tumor; CA 19-9; CA 125; CgA; multiple tumor markers

INTRODUCTION

In an attempt to detect cancer at an early stage in asymptomatic population, multiple tumor markers (TMs) were used for screening (1). We noticed in our early study that elevation of multiple TMs could also be detected in individuals without malignant disease. This led us to investigate whether multiple TMs are also helpful in detecting benign tumors that are at risk of developing into cancer. Two small groups of women with benign tumors, namely endometriosis and leiomyoma, were identified among those who were detected with elevated TMs.

Both endometriosis and leiomyoma are known to be risk factors for further development of malignancies. Patients with endometriosis have been known to be predisposed to the development of ovarian and uterine tumors whereas uterine leiomyomas are associated with an increased risk of developing uterine malignancies, particularly sarcomas (2). Recent evidence also indicates that having endometriosis itself may increase a woman's

Abbreviations: AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; PSA, prostate specific antigen including both free PSA+ PSA-ACT complex; CgA, chromogranin A; SCC, squamous cell carcinoma antigen; TM, tumor marker.

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risk of developing non-Hodgkin's lymphoma, malignant melanoma, and breast cancer (3).

Multiple circulating TMs that were measured during screening included alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), prostate-specific antigen (PSA including both free PSA+PSA-ACT complex), CA 125, CA 15-3, CA 19-9, squamous cell carcinoma antigen (SCC), and CgA. Among these, multiple TMs many have been known to be associated with specific types of cell; for example, CEA, PSA, CA 125, CA 15-3, and CA 19-9 are all associated with epithelial cell–derived carcinomas; AFP is associated with hepatocytes, CgA with neuroendocrine cells, and SCC with squamous cells. We found that in addition to CA 125, (4,5), elevation of two other TMs, namely CA 19-9 and CgA, were also detectable in both benign tumors. Surprisingly, many patients only had elevated CA 19-9 and CgA, without elevated CA 125. Our result suggests that elevated TMs can be found in benign gynecologic tumors such as endometriosis and leiomyoma and the elevation is not limited to CA 125. Elevated CA 19-9 and CgA could also be detectable even in the absence of elevated CA 125. Detection of these elevated TMs could be related to their risk of cancer development.

MATERIALS AND METHODS

Measurement of TMs

Serum levels of AFP, CEA, and PSA were determined by Abbott Architect 2000 (Abbott Park, IL). Levels of serum CA19-9, CA125, and CA15-3 were measured by an Abbott AXSYM instrument. SCC was determined by Abbott IMX. CgA was measured with an in-house enzyme-linked immunosorbent assay (ELISA) (6). The upper cutoffs for TMs are: 15 ng/mL for AFP, 5 ng/mL for CEA, 37 U/mL for CA 19-9, 4 ng/mL for PSA, 35 U/mL for CA 125, 30 U/mL for CA 15-3, and 100 ng/mL for CgA.

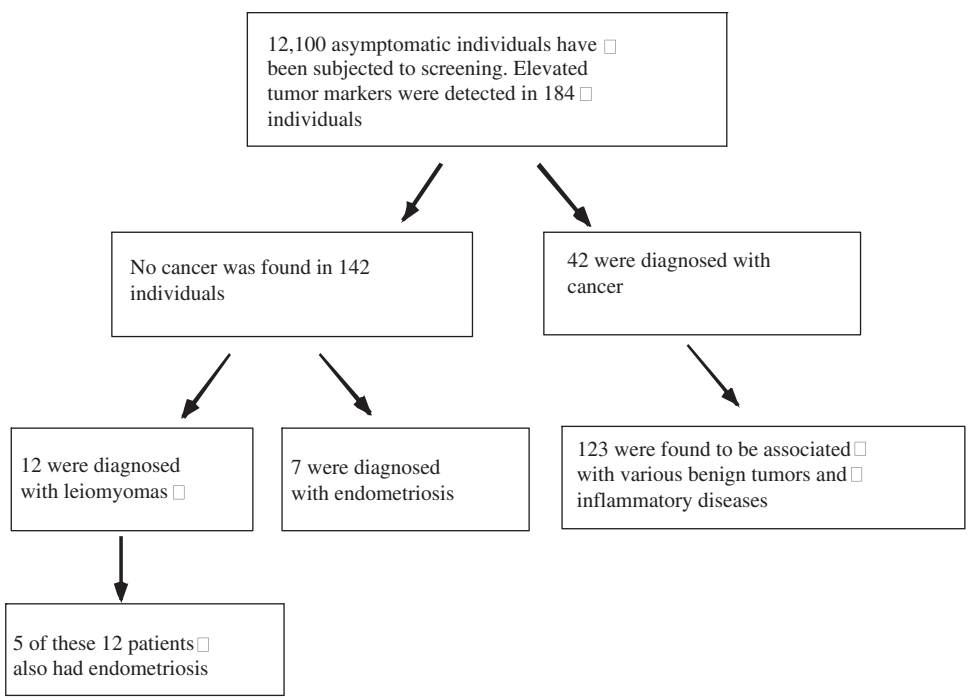
Screening Cohort

Study patients were among the 12,100 asymptomatic individuals who participated in screening with multiple TMs (1) (Chart 1), on a voluntary basis, in Chang Gung Memorial Hospital for their regular health checkup. A total of 184 individuals were detected with elevated TMs, were invited back to the hospital for revisit, and were examined in detail; 19 patients with endometriosis and leiomyoma were identified. There were 12 patients diagnosed with leiomyoma and seven patients with endometriosis. Among those 12 patients with leiomyoma, five of them also had endometriosis. The majority of the individuals participating were between 30 and 59 years old.

RESULTS

Elevation Found in Endometriosis

Elevated TMs were detected in all six patients with endometriosis (6/6, 100%) (Fig. 1A). In addition to CA 125, two patients had only elevated CA 19-9 and one



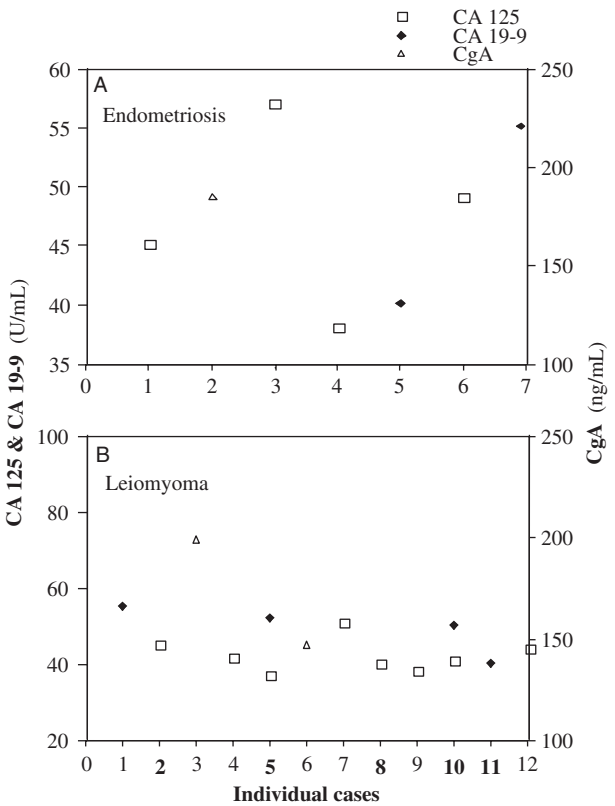


Fig. 1. Elevation of CA 125, CA 19-9, and CgA detected in endometriosis and leiomyoma. **A:** Elevated tumor markers detected in endometriosis. **B:** Elevated tumor markers detected in leiomyoma. Bold Arabic numbers for "Individual cases" indicate that both benign tumors were found in the same patient.

patient had only elevated CgA. Elevation of CA 125 remained the most frequently detected TM in endometriosis.

Elevation Found in Leiomyoma

Elevated TMs were detected in 92% of patients with leiomyoma (12/13) (Fig. 1B). However, five patients with leiomyoma also had endometriosis diagnosed at the same time. In addition to CA 125, elevated CA 19-9 and CgA were also detected in those patients with the diagnosis of only leiomyoma. It is interesting that only two patients with the diagnosis of both benign tumors simultaneously had both elevated TMs (CA 19-9 and CA 125), despite the fact that our investigation involved only a small number of subjects.

DISCUSSION

In this investigation, we learned that elevated TMs are detectable in benign tumors. The percentage of elevation was surprisingly high, with 100% in endometriosis and 92% in leiomyoma when multiple TMs were monitored. Since both endometriosis and leiomyoma are at risk of developing into cancer, it leads one to wonder whether the detection of elevation of TMs is associated with their cancer risk. It will be interesting to confirm, in the future, with a larger disease cohort, whether measuring TMs is useful not only in the management of cancer patients but whether it also has the potential of detecting cancer risk using multiple TMs.

We learned from screening of cancer with multiple TMs that each type of cancer is not associated with the elevation of a single but TMs related to different cell types (1). For example, not only AFP was detectable in hepatoma, one could also detect elevated CEA, CA 125, PSA, and CgA in liver cancer. At times among the elevated TMs detected in hepatoma the dominant TM AFP anticipated for hepatoma was absent. It is interesting to note that in these benign tumors we also found elevation in more than one type of TMs. Traditionally, CA 125 was the TM used in common benign gynecologic diseases such as endometriosis and uterine leiomyoma (5,7). However, in addition to CA 125, elevated CA 19-9 and CgA were also detectable and they were detected most of the time in the absence of the CA 125. Apparently, multiple TMs should be used in the management of even the benign tumor.

CgA is an interesting marker. We previously found that elevated CgA was always detected at the advanced stage of various carcinomas associated with a poor prognosis (8,9). It is not clear why we have detected CgA, a neuroendocrine cell-specific TM, in endometriosis and in leiomyoma. We need to determine, with a larger disease cohort in the future, whether detection of elevated CgA is associated with a greater cancer risk in these benign tumors.

We also noticed in this investigation that TMs detected in these benign tumors were not highly elevated. We did not detect any high levels of TMs commonly found in cancer. It appears that only low levels of of TM elevation are detectable at the early stage of cancer risk.

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