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ORIGINAL ARTICLE

The diagnostic value of tumor abnormal protein and high sensitivity C reactive protein in screening for endometrial cancer with endometrial thickness less than 8 mm*

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Abstract

Objective This study aimed to combine tumor abnormal protein (TAP) and high-sensitivity C-reactive protein (hs-CRP) level detection to diagnose endometrial cancer in patients with endometrial thickness less than 8 mm, and to provide a reference for clinical screening and diagnosis.

Methods Clinical data from 19 cases of endometrial cancer, diagnosed on the basis of pathological findings, were collected from September 2014 to December 2015. The inclusion criteria were as follows: the patients were first diagnosed with endometrial thickness less than 8 mm and were all in menopause. Perimenopausal patients (n = 26) with uterine fibroids seen during the same period were selected as a control group. Serum TAP and hs-CRP levels of the patients in the two groups were simultaneously determined on admission.

Results We found that both TAP and hs-CRP levels in the experimental group were higher than those in the control group [(182.95 ± 72.14) μm^2 vs. (133.19 ± 55.18) μm^2, P = 0.019; (7.52 ± 19.03) mg/L vs. (1.66 ± 2.31) mg/L, P = 0.136]. The sensitivity of TAP for the diagnosis of endometrial cancer was 73.68%, the specificity was 69.23%, and the Youden index was 0.4291. The diagnostic sensitivity and specificity of hs-CRP was 15.79% and 100%, respectively, and the Youden index was 0.1579. After plotting the receiver operating characteristics curves, the optimal cut-off value for TAP in diagnosing endometrial cancer was found to be 160.662 μm^2 and that for hs-CRP was 1.07 mg/L.

Conclusion For patients suspected of having endometrial cancer with endometrial thickness less than 8 mm, combined detection of TAP and hs-CRP levels can be used as a screening tool and can provide new ideas regarding clinical diagnosis and treatment.

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Key words: tumor abnormal protein (TAP); high-sensitivity C-reactive protein (hs-CRP); endometrial thickness; endometrial carcinoma

Endometrial cancer is a common gynecologic malignancy. Endometrial thickness is closely related to endometrial cancer. Currently, hysteroscopic biopsy is recommended to confirm the diagnosis for patients with endometrial thickness more than 8 mm on ultrasonography [1]. For patients with endometrial thickness less than 8 mm, follow-up is recommended and unnecessary hysteroscopy should be minimized. However, there are currently no known specific endometrial cancer markers; therefore, when endometrial thicknesses of less than 8 mm is found on ultrasonography, it is difficult to objectively formulate treatment programs [2]. Previous studies have reported that endometrial cancer may express abnormal protein (TAP) [3]. However, TAP has poor diagnostic specificity. This study aimed to combine detection of TAP and high-sensitivity C-reactive protein (hs-CRP) levels to diagnose endometrial cancer in patients with endometrial thickness less than 8 mm and to provide a

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reference for clinical screening and diagnosis.

Materials and methods

Material source and grouping

Clinical data from 19 cases of endometrial cancer, ultimately diagnosed based on pathologic findings, were collected from September 2014 to December 2015. The inclusion criteria were as follows: the patients were first diagnosed with endometrial thickness less than 8 mm and were all in menopause. In terms of pathological types, 17 cases were of adenocarcinoma, 1 case was of clear cell carcinoma, and 1 case of squamous cell carcinoma. In terms of degrees of differentiation, 4 cases were of high differentiation, 12 cases of moderate differentiation, and 3 cases of low differentiation. Perimenopausal patients (n = 26) with uterine fibroids, diagnosed during the same time period on the basis of pathological findings, were selected as the control group. The serum TAP and hs-CRP levels of patients in the two groups were determined on admission.

Measurement method

Fasting fingertip blood samples collected in the morning from patients of each group were obtained from the pathology department. Two slides of thin blood were prepared by pushing the blood across the slide and were kept still for drying. A special dropper was used to take the TAP detection reagent (Rising Medical Technology) and vertically drop 3 drops on each slide. The blood smear was kept still for 2 hours and re-dried to form "gathering spots". The slide was put under a TAP integrated chip-specific microscope (Rising Medical Technology). The "gathering spots" on the blood slices were sequentially scanned with an achromatic objective (× 4) and measured. At the same time, aggregates with abnormal forms were searched. The gathering spot diameter was used as the basic evaluation criteria: (1) 0–121 μm^2 and no obvious aggregates: normal TAP; (2) 121–225 μm^2 and smaller aggregates: abnormal TAP; (3) ≥ 225 μm^2 and relatively large aggregates: obviously abnormal TAP.

Fasting blood sample of patients in the inspection department was collected. The hs-CRP levels were measured using an immunoturbidimeter (GE automatic biochemical analyzer) according the reagent specification standards: (1) 0–10 mg/L: normal range and (2) > 10 mg/L: abnormal range.

Statistical methods

SPSS 17.0 was used to perform the chi-square test to detect differences between the groups for categorical data and the t test was used for continuous data. $P < 0.05$ was considered statistically significant. The diagnostic sensitivity refers to the correct determination of the proportion of actual patients with positive results and was calculated as: [number of true positive cases/(number of true positive cases + number of false negative cases)] × 100. The diagnostic specificity means the correct determination of the proportion of healthy people and was calculated as: [number of true negative cases/(number of true negative cases + number of false positive cases)] × 100. The Youden index is defined as the sum of sensitivity and specificity subtracted from 1. The Youden index ranges from 0 to 1, and a greater value indicates a higher diagnostic value. A receiver operating characteristic (ROC) curve was plotted to confirm the diagnostic value, which uses 1-specificity as the x-axis, and sensitivity as the y-axis. The cut-off value was obtained when the miter was 45°, and the sensitivity and specificity were good.

Table 1 Comparisons of clinical data between two groups

	Experimental group (n = 19)	Control group (n = 26)	P value
Age (years)	54.03 ± 6.01	52.23 ± 5.03	0.192
Menopausal duration	6.36 ± 3.57	5.94 ± 2.81	0.302
Gravidity	2.95 ± 1.54	2.78 ± 1.48	0.145
Parity	1.62 ± 0.92	1.57 ± 0.87	0.207
Vaginal bleeding or liquid discharge (Yes/No)	18/1	25/1	0.819

Results

No significant differences were found in age, menopausal status, pregnancy status, or clinical symptoms between the experimental and control groups, indicating that the indexes were comparable (Table 1).

The expression levels of TAP in the experimental group and control group were (182.95 ± 72.14) μm^2 and (133.19 ± 55.18) μm^2, respectively (P = 0.019). Fig. 1–3 show the expression levels of TAP in different pathological diagnoses. The expression levels of hs-CRP in both groups were (7.52 ± 19.03) mg/L and (1.66 ± 2.31) mg/L, respectively (P = 0.136).

By using recommended laboratory cutoff values as a standard, the sensitivity and specificity of TAP for the diagnosis of endometrial cancer were 73.68% and 69.23%, respectively, and the Youden index was 0.4291. The diagnostic sensitivity and specificity of hs-CRP were 15.79% and 100%, respectively, and the Youden index was 0.1579. The sensitivity and specificity of the combination of the two indexes were 77.83% and 69.23%, respectively, and the Youden index increased to 0.4706. However, using TAP and hs-CRP in a binary logistic regression analysis, the results showed that a positive result for TAP had a statistically significant predictive value for endometrial cancer (P = 0.014), but a positive result for hs-CRP had no statistical significance (P = 0.167). This illustrates that

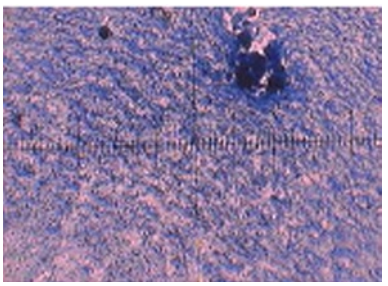

Fig. 1 Qi, uterine fibroids and a TAP level of 92.793 μm^2

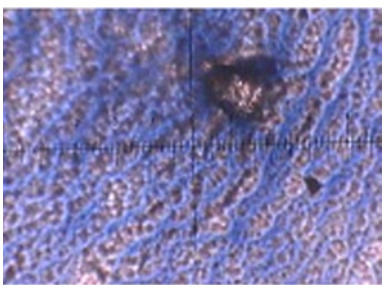

Fig. 2 Wan, moderate differentiated endometrial adenocarcinoma and a TAP level of 197.675 μm^2

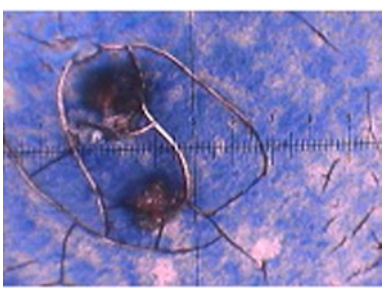

Fig. 3 Wang, poorly differentiated endometrial adenocarcinoma and a TAP level of 256.879 μm^2

a positive TAP result has a high predictive diagnostic value.

The ROC curves were used to analyze the screening and diagnostic value of TAP and hs-CRP for endometrial cancer in patients with endometrial thickness less than 8 mm. The areas under the curve (AUCs) for TAP and hs-CRP were 0.678 and 0.651, respectively. A TAP level > 160.662 μm^2 and hs-CRP level > 1.07 mg/L indicated possible endometrial cancer (Table 2 and Fig. 4).

Table 2 ROC curve analyzing the diagnostic values of TAP and hs-CRP

ROC curve parameters	TAP	hs-CRP
Area under the curve (AUC)	0.678	0.651
Youden index	0.4464	0.3423
Cut-off value	> 162.662	> 1.07
Sensitivity	63.16	65.00
Specificity	81.48	69.23
P value	0.0468	0.0704

Discussion

Endometrial cancer is one of the three gynecological malignancies and is an endometrial carcinogenesis [4]. In recent years, the incidence of endometrial cancer has increased gradually. As a result, early detection of and intervention in endometrial cancer has gained increasing attention from clinicians. At present, hysteroscopic biopsy is recommended to confirm the diagnosis for patients with endometrial thickness more than 8 mm, as measured on ultrasonography. For patients with endometrial thickness less than 8 mm, regular follow-up is recommended and unnecessary hysteroscopy should be minimized if no abnormal endometrial morphological changes are found and no symptoms associated with vaginal bleeding or abdominal [5] discomfort develop over long-term follow-up. However, clinically, there are still endometrial cancer patients with endometrial thickness less than 8 mm, and the consequences of omissions in these patients could be disastrous. For primary level health-care institutions in our country, serum marker levels for endometrial cancer should be particularly evaluated during screening, diagnosis, and timely intervention of endometrial cancer with obscure endometrial thickening.

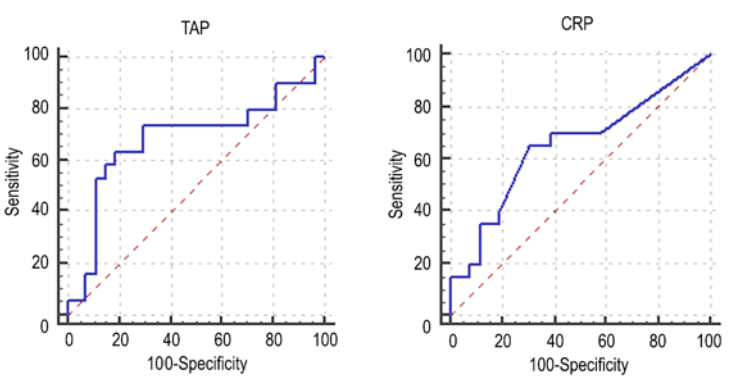

Fig. 4 ROC curve analysis of TAP and hs-CRP in endometrial cancer screening

TAP detection is a one-time combined detection of a variety of abnormal tumor sugar chain glycoproteins and involves aggregations of different glycoproteins to greatly amplify cancer signaling. Studies have reported that TAP has higher diagnostic values for a variety of digestive tract cancers [6–7], ovarian cancer [8], and bladder cancer [9]. TAP has also been reported to be expressed in endometrial cancer [3], with the level of TAP reflecting the endometrial cancer prognosis and recurrence [10], and can be a suitable serum marker for endometrial cancer.

hs-CRP is a clinically commonly used serum marker for the inflammatory response and tumors. hs-CRP can be highly expressed in a variety of diseases, but lacks specificity. One study reported that the hs-CRP level of patients with endometrial cancer after surgery significantly decreased compared with that before surgery [11], suggesting that hs-CRP may also be expressed in patients with endometrial cancer. Prior to this study, no method combined TAP and hs-CRP in screening for and diagnosing endometrial cancer.

In this study, all the included patients were first diagnosed with endometrial thickness less than 8 mm, but the diagnosis was confirmed as endometrial cancer. We found that the TAP and hs-CRP levels in the experimental group were both higher than those in the control group [(182.95 ± 72.14) μm^2 vs. (133.19 ± 55.18) μm^2, P = 0.019; (7.52 ± 19.03) mg/L vs. (1.66 ± 2.31) mg/L, P = 0.136]. The difference between the two groups in TAP level was statistically significant. By using the laboratory recommended cutoff value as a standard, the sensitivity of TAP for the diagnosis of endometrial cancer was 73.68%, specificity was 69.23%, and the Youden index was 0.4291. The diagnostic sensitivity and specificity of hs-CRP were 15.79% and 100%, respectively, and the Youden index was 0.1579. The sensitivity and specificity of the combined diagnosis of the two indexes were 77.83% and 69.23%, respectively, and the Youden index rose to 0.4706. However, the results of binary logistic regression analysis showed that a positive TAP result had a higher predictive diagnostic value (P = 0.014) than hs-CRP (P = 0.167) did.

After plotting the ROC curves, the optimal cut-off value for TAP to diagnose endometrial cancer was found to be 160.662 μm^2 and that for hs-CRP was 1.07 mg/L. The AUC of TAP was slightly higher than that of hs-CRP (0.678 vs. 0.651). Both of the indexes had moderate diagnostic value, and the diagnostic value of TAP was statistically significant. All the data suggest that TAP was more suitable for suspected positive endometrial cancer, while a negative hs-CRP result was more appropriate for excluding the diagnosis of endometrial cancer. However, the sample size of the study was relatively small; no long-term follow-up was conducted, and larger scale clinical trials are needed to confirm the conclusions.

In summary, for patients suspected of having endometrial cancer with endometrial thickness less than 8 mm, combined detection of TAP and hs-CRP levels can be used as a screening tool and can provide new ideas for clinical diagnosis and treatment.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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