The significances of joint-detection of serum CA125, HE4, SMRP and cytokines IL-8, IL-17 in patients with epithelial ovarian cancer

Zhu Pan1, Ma Rui2, Lei Mi3

1. Introduction

The incidence of ovarian cancer is next only to cervical cancer. Among these, epithelial ovarian cancer (EOC) was most common seen[1]. The early EOC, which is occult, don’t have obvious symptoms. So, most patients have been in advanced when found, whose 5 year survival rate has been less than 50%[2]. Therefore, effective early diagnosis and treatment is the key to improve the prognosis of patients. At present, Carbohydrate antigen 125 (CA125) and human epididymis protein 4 (HE4) for EOC detection are widely used in the clinical. However, there are few studies on the combination of soluble mesothelial related protein (SMRP), IL-8 and IL-7. This article analyzes the clinical significance of the joint detection of these 5 indicators in EOC, which is reported as follows.

Objective: To analyze the significances of joint-detection of serum CA125, HE4, SMRP and cytokines IL-8, IL-17 in patients with epithelial ovarian cancer. Methods: A total of 83 patients with ovarian tumor from May 2013 to May 2016 in our hospital were selected. Among these, there are 41 patients with EOC and 42 patients with benign ovarian tumor. At the same time, 42 cases of healthy people from health examination department were selected as control group. Expression levels of the 3 tumor markers and the 2 cytokines were compared. The levels of the 5 markers in the clinical pathological types and clinical stages of EOC were analyzed. Results: Serum CA125, HE4, SMRP and cytokines IL-8, IL-17 in EOC group were (258.47±54.09) U/L, (237.41±12.48) pmol/L, (7.36±2.17) nmol/L, (76.33±9.73) ng/mL, (23.89±7.12) pg/mL, respectively, which were higher than that in the benign ovary tumor group and healthy control group significantly. And the difference was considered to be statistically significant. Serum CA125, HE4, SMRP and cytokines IL-8, IL-17 in EOC patients with Pathological III-IV stage were (382.45±40.74) U/L, (276.19±46.13) pmol/L, (9.36±3.11) nmol/L, (89.06±4.27) ng/mL, (33.52±2.63) pg/mL respectively, which were higher than that in EOC patients with Pathological I-II stage significantly. And the difference was considered to be statistically significant. Serum CA125, HE4, SMRP and cytokines IL-8, IL-17 in EOC patients with serous type was significantly higher than that in EOC patients with mucinous type. And CA125, HE4, IL-8 in EOC patients with serous type were significantly higher than that in EOC patients with endometrial type. And the difference was considered to be statistically significant. Conclusion: The over expression of serum CA125, HE4, SMRP and cytokines IL-8, IL-17 in patients with epithelial ovarian cancer was related to pathological stage and pathological type, which is helpful to the early diagnosis and condition judgment.

Key words: Epithelial ovarian cancer Tumor markers Cytokines Detection significance
2. Materials and methods

2.1 General information

A total of 83 patients with ovarian tumor from May 2013 to May 2016 in our hospital were selected. Among these, there are 41 patients with EOC and 42 patients with benign ovarian tumor. All patients were diagnosed by operation, needle biopsy or postoperative pathology. In the EOC group, the patients aged from 19 to 74 years old. FIG staging: there were 19 cases of stage I-II and 22 cases of stage III-IV. Tissue typing: There were 20 cases of serous adenocarcinoma, 17 cases of mucinous adenocarcinoma, and 4 cases of endometrioid carcinoma. Pathological grading: There were 7 cases of moderate and high differentiated G1 stage, 13 cases of moderately differentiated G2 stage, 20 cases of poorly differentiated G3 stage and 1 case of undifferentiated G4 stage. These patients have not received radiotherapy and chemotherapy before operation. In the benign ovarian tumor group, the patients aged from 20 to 75 years old. There were 29 cases of oophoritic cyst, 6 cases of dermoid tumor, 3 cases of fibro cellular tumor and 4 cases of inflammatory mass. At the same time, 42 cases of healthy people from health examination department were selected as control group, aged from 20-75 years old. Exclusion criteria: patients taking drugs or other treatments; with seriously infect; with other organic pathological changes; with congestive heart-failure and with severe complications. This study was approved ethics committee in our hospital. And all patients have signed the informed consent.

2.2 Specimen collection and detection method

5 mL of fasting peripheral venous blood of all patients were selected and placed into the heparinized anticoagulative tube (1:20 U), centrifugation for 15 min at the speed of 3 000 rpm, isolated serum and stored in -80 ℃ refrigerator. Serum CA125 was detected by chemiluminescence. The kits were purchased from American Beckman Coulter Company. HE4, SMRP, IL-8 and IL-17 were detected by ELISA. The kits were purchased from American R&D company. The operation process was performed according to the instruction strictly. Normal reference range of CA125: < 35 U/L; normal reference range of HE4: < 75 pmol/L, SMRP < 1.5 nmol/L. Normal reference range of IL-8: < 52 ng/mL and normal reference range of IL-17 < 5.5 pg/mL[3,4]. 3 tumor markers and the expression levels of the 2 cytokines were compared between EOC group, benign ovary tumor group and control group. The difference of the 5 markers was compared between different clinicopathological types and clinical stages of EOC.

2.3 Statistical methods

SPSS 21.0 statistical package was conducted for statistical analysis. Relevant data indexes were described as mean ± standard deviation. The means comparison between the two samples was done by the t-test. And counting material used a chi-square test. Values of P<0.05 were considered to be statistically significant.

3. Results

3.1 Analysis of 3 tumor markers and the expression levels of 2 cytokines between the 3 groups

Serum CA125, HE4, SMRP and cytokines IL-8, IL-17 in EOC group were (258.47±54.09) U/L, (237.41±12.48) pmol/L, (7.36±2.17) nmol/L, (76.33±9.73) ng/mL, (23.89±7.12) pg/mL, respectively, which were higher than that in the benign ovary tumor group and healthy control group significantly. And the difference was considered to be statistically significant (P<0.05). The comparison of indexes between benign ovary tumor group and healthy control group was not considered to be statistically significant (P>0.05). See table 1

3.2 Comparison of 3 tumor markers and the expression levels of 2 cytokines between EOC patients with different pathological stages

Serum CA125, HE4, SMRP and cytokines IL-8, IL-17 in EOC patients with Pathological III-IV stage were (382.45±40.74) U/L, (276.19±46.13) pmol/L, (9.36±3.11) nmol/L, (89.06±4.27) ng/mL, (33.52±2.63) pg/mL respectively, which were higher than that in EOC patients with Pathological I-II stage significantly. And the difference was considered to be statistically significant (P<0.05). See table 2.

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**Table 1.** Analysis of 3 tumor markers and the expression levels of 2 cytokines between the 3 groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>CA125 (U/L)</th>
<th>HE4 (pmol/L)</th>
<th>SMRP (nmol/L)</th>
<th>IL-8 (ng/mL)</th>
<th>IL-17 (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EOC group</td>
<td>41</td>
<td>258.47±54.09</td>
<td>237.41±12.48</td>
<td>7.36±2.17</td>
<td>76.33±9.73</td>
<td>23.89±7.12</td>
</tr>
<tr>
<td>benign ovary tumor group</td>
<td>42</td>
<td>22.65±5.82</td>
<td>36.62±6.11</td>
<td>1.19±0.22</td>
<td>51.25±3.17</td>
<td>4.34±1.07</td>
</tr>
<tr>
<td>healthy control group</td>
<td>42</td>
<td>20.16±3.19</td>
<td>33.95±5.05</td>
<td>0.93±0.17</td>
<td>50.34±2.84</td>
<td>3.98±0.85</td>
</tr>
</tbody>
</table>

Note: compared with EOC group, *P<0.05.

**Table 2.** Comparison of 3 tumor markers and the expression levels of 2 cytokines between EOC patients with different pathological stages.

<table>
<thead>
<tr>
<th>Pathological stages</th>
<th>n</th>
<th>CA125 (U/L)</th>
<th>HE4 (pmol/L)</th>
<th>SMRP (nmol/L)</th>
<th>IL-8 (ng/mL)</th>
<th>IL-17 (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-II</td>
<td>19</td>
<td>72.54±5.74</td>
<td>112.36±12.58</td>
<td>4.21±1.03</td>
<td>73.07±3.74</td>
<td>21.57±2.49</td>
</tr>
<tr>
<td>III-IV</td>
<td>22</td>
<td>382.45±40.74</td>
<td>276.19±46.13</td>
<td>9.36±3.11</td>
<td>89.06±4.27</td>
<td>33.52±2.63</td>
</tr>
<tr>
<td>T value</td>
<td></td>
<td>120.02</td>
<td>83.011</td>
<td>3.492</td>
<td>6.631</td>
<td>7.008</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>
Table 3.
Comparison of 3 tumor markers and the expression levels of 2 cytokines between EOC patients with different pathological types.

<table>
<thead>
<tr>
<th>Pathological types</th>
<th>n</th>
<th>CA125 (U/L)</th>
<th>HE4 (pmol/L)</th>
<th>SMRP (nmol/L)</th>
<th>IL-8 (ng/mL)</th>
<th>IL-17 (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>serous type</td>
<td>20</td>
<td>421.5±42.62</td>
<td>407.3±62.17</td>
<td>8.89±1.42</td>
<td>83.8±5.78</td>
<td>31.8±2.74</td>
</tr>
<tr>
<td>mucinous type</td>
<td>17</td>
<td>92.0±10.74</td>
<td>121.9±15.22</td>
<td>4.34±2.07</td>
<td>70.8±4.49</td>
<td>20.8±6.27</td>
</tr>
<tr>
<td>endometrial type</td>
<td>4</td>
<td>116.4±21.18</td>
<td>320.8±58.24</td>
<td>7.98±1.85</td>
<td>72.5±4.69</td>
<td>30.1±2.81</td>
</tr>
</tbody>
</table>

Note: compared with mucinous type, *P*<0.05; compared with endometrial type, **P**<0.05.

3.3 Comparison of 3 tumor markers and the expression levels of 2 cytokines between EOC patients with different pathological types

Serum CA125, HE4, SMRP and cytokines IL-8, IL-17 in EOC patients with serous type was significantly higher than that in EOC patients with mucinous type. And CA125, HE4, IL-8 in EOC patients with serous type were significantly higher than that in EOC patients with endometrial type. And the difference was considered to be statistically significant (*P*<0.05). CA125, HE4, SMRP, IL-17 in EOC patients with endometrial type were higher than that in EOC patients with mucinous type. And the difference was considered to be statistically significant (*P*<0.05). See table 3.

4. Discussion

EOC is one of the most common gynecologic malignant tumors, without obvious symptoms, which is occult. The 5 year survival rate was as high as 92% before the cancer cells were transferred. However, most patients have been in advanced when found, whose 5 year survival rate has been less than 50%[5]. Therefore, effective early diagnosis and treatment is the key to improve the prognosis of patients. Tumor markers are substances secreted or exfoliated by tumor cells, or specific antigens produced by the body against tumor cells, which can be released into the body fluid circulation[6]. In recent years, with the increased incidence of malignant tumors, tumor markers are more and more widely studied in medical research. However, a single tumor marker is not sensitive enough to meet the need of the diagnosis. The combined diagnosis of various tumor markers can overcome the occurrence of misdiagnosis and missed diagnosis, which can improve the accuracy of diagnosis.

CA125 is a high molecular weight glycoprotein secreted by epithelial cell in the embryonic development period. And it is the first choice of tumor marker for ovarian cancer. It will not secrete under normal regulation. It expressed on the cell surface and secreted into the blood when ovarian malignant disease occurred. And large secretion of CA125 appeared in the serous EOC[7,8]. Clinical studies have shown that CA125 was closely related to the occurrence and development of EOC. It has high sensitivity but low specificity. In ovarian benign diseases such as ovarian cyst, endometriosis and even lung cancer, CA125 also will increase abnormally. If it was taken as a tumor marker, it would be prone to false positive results. All these will result in misdiagnosis[9]. The results of this study indicated that the value of CA125 in patients with EOC can reach to (258.47 ± 54.09) U/L, which was significantly higher than that of benign ovarian tumor group and healthy control group. CA125 is a protease inhibitor in sperm maturation, which is the highest expression in male epididymis[10]. The expression sites of HE4 in female are genital epithelium. The study found that HE4 highly expressed in EOC and didn’t express in normal ovarian tissue, which showed that HE4 can be a new type of tumor marker. In addition, studies have shown that HE4 has higher diagnostic value than CA125 in early screening of EOC[11,12]. The results of this research showed that the value of HE4 in serum in patients with EOC was up to (237.4±12.48) pmol/L, which was significantly higher than that of benign ovarian tumor group and healthy control group, which showed that HE4 can be a new potential tumor marker. And it was of great value for screening and diagnosing EOC. Mesothelin is a tumor marker antigen discovered in recent years, which expressed in mesothelial cells of body cavity surface in normal body. SMRP is a soluble mesothelin related protein, heterogeneous mesothelin[13,14]. Studies have shown that the level of SMRP in EOC significantly increased. The results of this study showed that the SMRP level in patients with EOC was significantly higher than that in benign tumor group and healthy control group, which was up to (7.36±2.17) nmol/L. All theses confirmed that it was significantly elevated in EOC patients. The results of this study showed that CA125, HE4 and SMRP expressed most in serous EOC, followed by endometrioid type, the lowest expression in patients with mucinous EOC. All the three expressed highly in the pathological III-IV stage.

IL-8 is the chemotactic factor of ELR+CXC, which can be expressed by mononuclear macrophages, lymphocytes, neutrophile granulocytes and other lymphocytes[15]. Many researchers have showed that the high expression of IL-8 was related to unfavorable prognosis of many malignancies. IL-8 can enhance the reproductive capacity of cancer cells by activating multiple signal transduction pathways, such as promoting the expression of cyclin Cyclin D1 and Cyclin B1, which promotes cell transformation from G to S. It, indicated that IL-8 could promote the proliferation of cancer cells by regulating the distribution of cell cycle[16-18]. In addition, studies have shown that IL-8 can accelerate apoptosis by increasing the activity of Caspase-3 for maintaining the proliferation of EOC cells. The results of this study showed that IL-8 in patients with EOC was (76.3±9.73) ng/mL, which was significantly higher than that
in benign ovarian tumor group and healthy control group. It may maintain the continuous proliferation ability of EOC cells through the mechanisms above.

IL-17 is a kind of strong activity of proinflammatory cytokines secreted by Th17 cells, which has the role of regulating inflammation. IL-17 amplifies the inflammatory response by synergistic action with a variety of cytokines[9]. Recent researches showed that in peripheral serum of cancer patients, Th17 cells and IL-17 increased significantly, such as liver cancer, colon cancer and prostate cancer. It may be that IL-7 induced angiogenesis by regulating the secretion of vascular endothelial growth factor (VEGF) in fibroblasts and stromal cells, which promotes the growth and metastasis of tumor cells[20-22]. We found that IL-17 in peripheral blood of patients with EOC was as high as (23.89 ± 7.12) pg/mL, which was significantly higher than that in benign tumor group and healthy control group. The results of this study showed that IL-8 and IL-17 expressed most in serious EOC, followed by endomeitioid type, the lowest expression in patients with mucinous EOC. Both of the two expressed highly in the pathological III-IV stage.

In conclusion, the over expression of serum CA125, HE4, SMRP and cytokines IL-8, IL-17 in patients with epithelial ovarian cancer was related to pathological stage and pathological type, which is helpful to the early diagnosis and condition judgment. In the future study, we will focus on the determination of tumor markers in different periods, and further analyze the mechanism of the tumor markers in order to provide a theoretical basis for the diagnosis of EOC.

Reference


