Evaluation of soluble intracellular adhesion molecule-1 (sICAM-1) in benign and malignant ovarian masses

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Summary

Purpose: To evaluate serum ICAM-1 levels preoperatively in patients with ovarian masses.

Methods: Estimation by ELISA assay in 101 women with pelvic tumours and 16 healthy controls was performed. Correlations of sICAM-1 levels with CA-125, Tumour Volume Index, morphological score and pathological findings were studied.

Results: Fifty-one ovarian tumours were malignant, five were borderline and 45 benign. Mean levels of sICAM-1 were respectively, 311.1 ± 182.9 ng/ml, 172.6 ± 40.1 ng/ml, 241.8 ± 74.1 ng/ml and 195.6 ± 68.7 ng/ml for controls. The area under ROC curve for sICAM-1 was 0.72 (95% CI 0.58-0.82), the cut-off 250 ng/ml, corresponding to 81.3% sensitivity and 52.9% specificity. Serum ICAM-1 correlated with morphological score ($r = 0,51$, $p < 0.001$), but not with FIGO stage, tumour grade, Tumour Volume Index and CA-125.

Conclusion: sICAM-1 concentrations are higher in patients with malignant tumours, but poorly correlate with clinical status. The clinical use alone in ovarian malignancy detection and tumour differentiation seems to have limited application. Combinations of CA-125 and sICAM-1 could improve the test characteristics.

Key words: ICAM-1; Ovarian; Cancer; Benign; Borderline tumour.

Introduction

Ovarian cancer is the fourth most frequent cause of death among women and five-year survival independent of the clinical stage amounts to approximately 30%. In spite of the diagnostic development, 75% of all detected cancers are in more advanced stages (III and IV according to FIGO). A late diagnosis has a great influence on the possibilities of the therapy and a poor prognosis. The early stages of this neoplasm are typically asymptomatic and there is a need to develop new standards for early detection.

Ultrasonography is one of the most used methods with a good sensitivity, but insufficient specificity. The determination of CA-125 levels is practically limited to advanced stages and monitoring of patients with ovarian cancer. Several new substances, including adhesion molecules and cytokines, have been reported to be useful in detecting or monitoring patients with different malignancies. Intracellular adhesion molecule-1 was found to be elevated, but not specifically, in lung, colon, breast and bladder cancer, and melanoma [1-7].

The aim of our study was to evaluate serum concentrations of intracellular adhesion molecule-1 in patients with ovarian masses.

Materials and Methods

The study included 101 women treated surgically in our departments because of suspicious pelvic tumours and 16 healthy women (control group). Healthy subjects were examined by internists and had multiple laboratory tests performed to exclude essential or current diseases. Patients qualified for surgery were examined gynaecologically and with transvaginal ultrasonography (ALOKA SSD5500, transvaginal 5 MHz and abdominal 3.5 MHz head). We estimated morphological score according to Ferazzi [8] and the Tumour Volume Index (TVI = AxBxCx0.523) to facilitate statistical analysis. The serum samples were obtained from both groups, centrifuged five minutes at 3000 rpm and assayed for CA-125 (AXSYM Abbot Lab., USA) and partially stored frozen until the whole material was completed. The sICAM-1 levels were assayed in duplicate using the Parameter® Human sICAM-1 Kit (R&D Systems, USA) on Dynex MRX 1.33 Reader (UK). The detection limit of this assay was 0.35 ng/ml according to the manufacturer. Intra-assay precision did not exceed 9.1%. Material from surgical treatment was verified by pathological examination, including grading (G) and FIGO staging when a malignant process was diagnosed. The Mann-Whitney test, Spearman test and Pearson correlation coefficient were used for statistical analysis performed on SigmaStat v2.0 (Jandel Corp, USA). Receiver Operating Characteristic Curves were calculated and analysed using ROCKit v0.9, according to the methodology of Metz *et al.* [9] We assumed $p < 0.05$ as statistically significant.

Results

According to the pathological findings patients were divided into three groups: with malignant tumour of the ovary, borderline tumour and benign. The fourth group consisted of healthy controls. Mean age in the groups was respectively: 51.5 ± 11.5 (range 23-80), 46.0 ± 15.8 (range 25-62), 39.4 ± 14.3 (range 13-71) and 27.8 ± 12.6 (range 20-63). Mean Body Mass Index (BMI) in groups varied from 23.4 to 27.1, but the differences were not sta-

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tistically significant. Among 51 patients with pathologically diagnosed malignant ovarian processes 25 cancers were serous, seven mucinous and seven solid, five endomtrioid; the rest included anaplastic and clear-cell cancer as well as dysgerminoma, Krukenberg and endodermal tumor. All five cases of borderline tumours were serous. Benign masses were pathologically identified as serous cysts (n = 15), endometrioid cysts (n = 12), teratomas (n = 9), inflammatory tumours (n = 6) and fibrothecomas (n = 3). Malignant tumours were mostly in advanced Stages III (n = 29) and IV (n = 7) according to FIGO classification; only 14 were in Stage I and one in Stage II. Cut-off level for CA-125 was 35 U/ml.

To delineate discrimination for statistical analysis we calculated the cut-off for sICAM-1 by the ROC curve including healthy women and those with malignant ovarian tumours. The best fit was 250 ng/ml, corresponding to 81.3% sensitivity and 52.9% specificity. Mean concentrations of CA-125 and sICAM-1 are presented in Table 1 with only statistically significant differences pointed out. Correlations of CA-125 and sICAM-1 with FIGO stage, grading, TVI and morphological index among patients with ovarian malignancies are presented in Table 2. There was also no statistically significant correlation between sICAM-1 and CA-125 concentrations (Figure 1). Even when serous and non-serous tumours were analysed separately, no correlation was found.

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CA-125 in detecting malignancy were respectively: 93.8%, 74.5%, 53.6% and 97.4%. The sensitivity, specificity, PPV and NPV of detecting a malignant ovarian mass using sICAM-1 were respectively: 81.3%, 52.9%, 35.1% and 90.0%. When both tests were used together, increased specificity, PPV and NPV were estimated, reaching respectively 93.8%, 86.3%, 68.2% and 97.8%. The discrimination power in detecting malignancy is presented as the ROC curve (Figure 2), for CA-125 area under curve is 0.85 (95% CI, 0.75-0.92) and for sICAM-1 0.72 (95% CI, 0.58-0.82). A parallel ROC curve for malignant and benign mass discrimination is presented in Figure 3. Area under the ROC curve for CA-125 is 0.78 (95% CI, 0.68-0.86) and for sICAM-1 0.63 (95% CI, 0.51-0.73).

Table 1. — *Mean (± SD) concentrations of CA-125 and sICAM-1 in four groups of patients.*

	CA-125 (U/ml)	sICAM-1 (ng/ml)
Malignant tumour	713.0 ± 1159.9[a, b]	311.1 ± 182.9[c, e]
Borderline tumour	93.3 ± 145.4	172.6 ± 40.1[e]
Benign tumour	72.6 ± 187.8[b]	241.8 ± 74.1[d]
Control group	14.8 ± 8.5[a]	195.6 ± 68.7[c, d]

Data presented as means ± SD (Standard Deviation), *, **, +, ++, +++ → were used to show two groups, where the difference was statistically significant, in example * is pointed in: malignant tumor and control group for CA125. If the table is not clear, I propose to change symbols used as follows: * → a, ** → b, + → c, ++ → d, +++ → e, suggested table.
[a] and [b] Mann-Whitney test $p < 0.001$; [c] Mann-Whitney test $p = 0.009$; [d] Mann-Whitney test $p = 0.033$; [e] Mann-Whitney test $p = 0.017$.

Table 2. — *Correlations of CA-125 and sICAM-1 with disease stage, tumour grade, volume index and morphological score.*

Spearman's test	CA-125 (U/ml)	sICAM-1
FIGO stage	R = 0.58, p < 0.001[*]	NS
Grading (G)	NS	NS
TVI	NS	NS
Morphological score	NS	R = 0.45, p = 0.003[**]

NS - not significant; [*] Pearson's correlation coefficient r = 0.21, p = 0.15, not significant; [**] Pearson's correlation coefficient r = 0.51, p < 0.001.

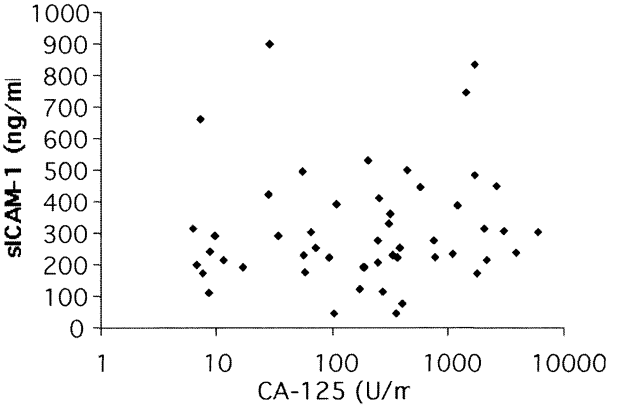

Figure 1. — Lack of correlation between sICAM-1 and CA-125 in patients with ovarian malignancies.

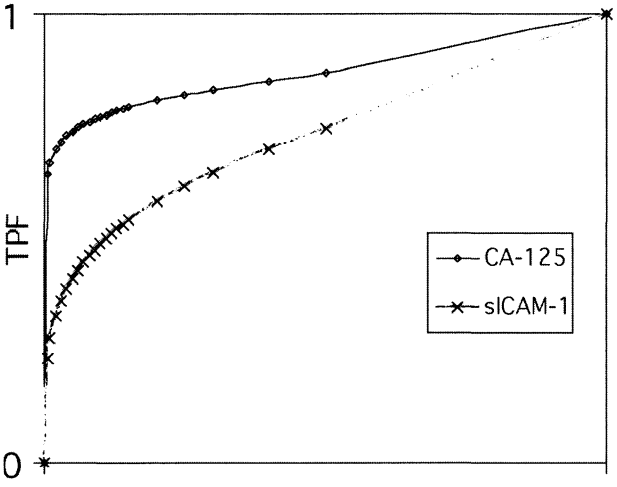

Figure 2. — ROC curve analysis in detecting malignant process.

Discussion

Overexpression of ICAM-1 is one of the possible mechanisms of NK cell suppression, the pathway to overcome immunological surveillance of tumour growth [10]. Constitutive production of ICAM-1 by tumour cells was proven to be auto- and paracrine growth stimulator as well as neovascularisation stimulator, but also opposite opinions can be found in the literature [1, 10].

The mean concentration for healthy controls in our study was lower than that reported by others [2, 5, 6]. Mean concentrations of sICAM-1 in malignant tumours

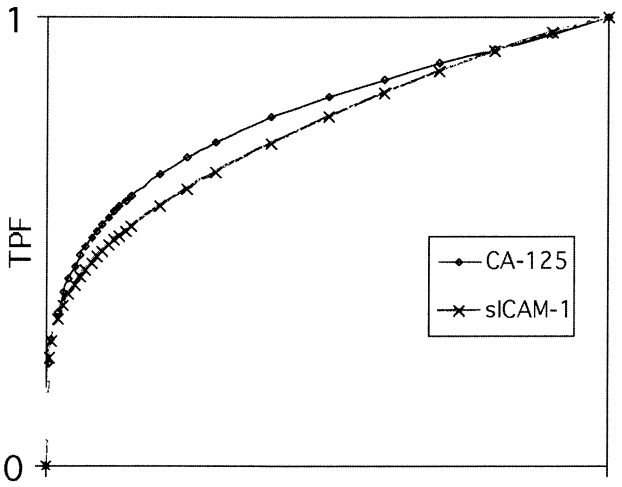

Figure 3. — ROC curve analysis in discriminating between benign and malignant masses.

were similar to other studies [2, 3, 6, 11] and were higher than in controls. Theoretically higher expression of ICAM-1 in malignancies should result in higher concentrations of its soluble form. We could prove this, but no other correlation with stage of the disease, tumour size or differentiation grade was observed. Recent histochemical analyses suggest that intensive ICAM-1 production occurs in early stages of carcinogenesis, and there is a relative decrease in ICAM-1 production during tumour growth [7]. Many other authors found no correlation of sICAM-1 with cancer size or grading [3-5, 11]. Moreover Sprenger *et al.* did not find a correlation of sICAM-1 with disease stage in lung cancer [2].

Interestingely bone and liver metastases were well predicted by sICAM-1 concentrations [3, 5]. Lung metastases were also reported to be correlated with higher sICAM-1 levels [4]. We did not observe any statistically significant difference in patients with disseminated disease Stage IV according to FIGO.

The power of sICAM-1 in discriminating malignant tumours from healthy controls was 0.72 in ROC analysis, a bit lower than reported by Callet *et al.* (0.758) [11]. The cut-off level from the ROC analysis was 250 ng/ml. In another study it was reported to be 235 ng/ml – nearly the same as our cut-off calculated as a 95% confidence interval of controls (data not shown) [11]. The same study reported a correlation of sICAM-1 with CA-125 in patients with non-serous ovarian cancer, which could not be proven in our study [11]. However the lack of correlation of sICAM-1 with CA-125 results in detection of ovarian cancer in some cases, where CA-125 is within normal range. As in our study it could detect some cases of cancer leading to improvement of the combined CA-125 and sICAM-1 test.

On the other hand the possibility of preoperative discrimination between benign and malignant ovarian masses also seems to be limited. The ROC analysis qualifies sICAM-1 estimation as a poor test for differentiation. Similar results were also reported by Darai *et al.* [12] Reassuming, it appears that circulating ICAM-1 concentrations do not provide much information for the preoperative evaluation of patients with ovarian masses.

Conclusion

Serum ICAM-1 concentrations are higher in patients with malignant ovarian tumours, but correlate poorly with clinical status. The clinical use of sICAM-1 estimation alone in ovarian malignancy detection and tumour differentiation seems to have limited application. Combinations of CA-125 and sICAM-1 could improve the test characteristics.

Acknowledgements

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