SPECIFIC FEATURES OF THE STROMAL OVARIAN TUMORS

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CHARACTERISTICS OF THE STROMAL OVARIAN TUMORS (Abstract): Aim of the study: establishing a characteristic pattern for the stromal ovarian tumors. Material and methods: we realized the clinical-statistics analyze of 27 stromal tumors (lot B) from a total of 498 patients with ovarian tumors (lot A), diagnosed and treated between 1999 – 2008 in Elena Doamna Hospital of Obstetrics and Gynecology, Iasi. We used the clinical files of these patients, operatory protocols and anatomopathological results. Results: we analyzed a large number of parameters: age, location, first diagnoses, symptoms, anatomopathological diagnose, immunohistochemical diagnose, etc. When we compared the two lots of patients we pointed out significant differences for the following parameters: most affected group of age, first diagnose, and associated diseases, anatomopathological and immunohistochemical differences, and prognostic factors. Conclusions: stromal ovarian tumors are a less studied entity, with particular anatomopathological and immunohistochemical features which differentiates them from the rest of the ovarian tumors. Keywords: OVARIAN CARCINOMA, TUMOR, BIOMARKER

The malignity of stromal ovarian tumors is somehow between the same characteristics as in the case of the epithelial tumors. Based on histological grading it will be appreciated the tumoral invasion, short term prognostic, type of surgical procedure and its necessity, future oncologic protocol (1, 3, 4, 6, 7).

The interaction between tumor and ovarian stroma is an insufficient aspect of ovarian tumorogenesis. Tumoral aria, including stromal fibroblasts, infiltrative stromal cells, vascular and lymphatic network and extracellular matrix is an integrated part of carcinogenetic process, promoting cellular growth and metastatic disorders (1, 2, 5).

Stromal alterations which accompany the tumoral progression include breaches in basal membrane which surrounds the tumor, severe immune response and angiogenesis (new vascular network). Additional breakdowns of the mesenchymal connective tissue surrounding the tumor can also be noted (6, 7, 9, 10, 11). These changes resemble a lot with tissular response observed during the healing of wounds through fibrosis (8, 10, 11). Fibroblasts and their role in tumorogenesis are considered to be the new target in the development of
new therapies for the tumoral stroma (10, 11), tumor associated fibroblasts or their disturbed environment (8, 10).

Unfortunately today we have less information regarding the stromal ovarian fibroblastic activation because of the lack of a performant experimental research system.

Our study recognizes the implication of a double interaction between neoplastic cells and ovarian peritumoral stroma, demonstrating their relationship in sustaining and promoting the tumoral invasion. After the analyze of the two lots of patients and the correlation of data with the medical literature we realized a protocol based on the conclusions of this study.

MATERIAL AND METHODS

This personal study was realized in multiple directions (anatomical, clinical, statistical and anatomopathological) using the following components: 1. we realized a retrospective study on 498 patients hospitalized in Clinical Hospital of Obstetrics and Gynecology “Elena Doamna” Iasi, between 1.01.1999 – 31.12.2008. The lot of 498 patients with ovarian pathology was selected from the total of 8898 general gynecological pathology; 2. lot A represents all patients diagnosed with ovarian tumors, meaning all 498 cases; 3. lot B represents patients with stromal ovarian pathology, selected from all cases; 4. microscopic study was realized on paraffin included specimens selected from the lots of study (we selected patients from all groups of age with/without other associated pathology); 5. macroscopic histopathological study followed the macroscopic aspect of all tumors, local extension, stages; 6. microscopic histopathological study evaluated the specimens colored with HE for establishing the diagnose of organ and after that anatomopathological diagnose; 7. imunohistochemical study used an indirect tristadal method and a panel of 5 antibodies: ER (estrogen receptor), PR (progesterone receptor), S100 (protein S100), SMA (smooth muscle actin) and Caldesmon. We realized dosage for 18 ovaries (for ovarian tumors in generally) and for 3 stromal ovarian tumors; 8. Statistic analyze used many methods: t-Student test, test $\chi^2$, relative risk, predictive value and tendency. Data was followed up and charged with statistic functions from Excel and EpInfo.

RESULTS AND DISCUSSION

Lot A contains all 498 cases of ovarian pathology, representing 5.6% from all 8898 patients with gynecological pathology hospitalized between 1999-2008. Lot B contains 27 stromal and sex cords ovarian tumors: 7 granulosa tumors (one bilateral and one cystic) (26%), 11 ovarian fibromas (41%), one ovarian thecoma (4%), 5 ovarian fibrothecomas (18%), 3 ovarian mixomas (11%).

The distribution on group of age for lot A reveals: highest frequency for group 31-40 years (26.51%), closely followed by group 41-50 years (21.08%). For lot B the age average is 45.5 years, between the intervals 22-69 years. The result is congruent with the result from group A, 45.94 ± 15.68 years (t-Student=0.15; dF=496; p>0.05). The distribution on group of age for lot B reveals following aspects: highest frequency: 41-50 years (33.33%), followed by group 51-60 years (22.23%); the rest of the groups do not have frequency variations, each of the containing four cases (14.8%).

Comparing the associated co morbidities we can highlight a difference between the two lots: for lot A most associated were
cardiovascular diseases (30.8%), and for lot B genital pathology (47%).

Comparing clinical diagnose for the two lots we pointed out the following elements: patients from lot A had associated pain (100%), while lot B 98%; bleeding for lot A: 0.6% and for lot B: 28%.

For stromal ovarian tumors we followed many steps for ultrasound exam also: we wanted to correlate the ultrasound aspect with the histological subtype of the tumor; increased echogenity with posterior shadow suggested ovarian fibroma while diffuse echogenity without posterior shadow was correlated with pure thecoma; echodense tumors, without posterior shadow suggested fibrothecoma.

The analyze of CA 125: lot A revealed following aspects: malignant tumors had average values (163.63 ± 143.08 UI/ml) for stage II, borderline tumors had average values (39.59 ± 10.0 UI/ml) for stage I, benign tumors had average values (27.21 ± 18.22 UI/ml) for normal interval. Only one teratoma was evaluated (66.5 UI/ml). Stromal tumors were most of the cases in stage I (96± 106 UI/ml). For lot B we pointed out the following aspects: granulosa tumors had average values (111.6 ± 75.4 UI/ml) for stage I, for the rest of the tumor types the values were under the limit of 35 UI/ml (tab. I).

### TABLE I

**Correlation matrix of average values for CA 125 for different stromal ovarian tumors**

<table>
<thead>
<tr>
<th>Tumors</th>
<th>granulosa (n=7)</th>
<th>ovarian fibroma (n=11)</th>
<th>ovarian thecoma (n=1)</th>
<th>fibrothecom (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ovarian fibroma (n=11)</td>
<td>2.56 (p&lt;0.05)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ovarian thecoma (n=1)</td>
<td>2.95 (p&lt;0.05)</td>
<td>2.54 (p&lt;0.05)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>fibrothecom (n=5)</td>
<td>2.85 (p&lt;0.05)</td>
<td>1.39 (p&gt;0.05)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>mixom (n=3)</td>
<td>3.10 (p&lt;0.05)</td>
<td>3.57 (p&lt;0.01)</td>
<td>0.43 (p&gt;0.05)</td>
<td>1.36 (p&gt;0.05)</td>
</tr>
</tbody>
</table>

We dosed CA125 for the patients with clinical and ultrasound suspicion of neoplastic tumor. We had values inside the normal interval but also very increased values, over 400 UI/ml. The evolutive stages of malignant tumors for which CA125 was positive were in most of the cases terminal stages, with distance and epiploic dissemination.

Macroscopic anatomopathological exam offered important details regarding the aspect of the tumor, shape, consistence, colour. The lab dissection of the specimens revealed the inside aspect, described the content (color, aspect, consistence, volume), septum and intratumoral vegetations.

Microscopic anatomopathological exam pointed out the invasion of ovarian stroma in benign and malign tumoral processes. The histological fragments were prelevated from different ovarian sites.

Imunohistochemical evaluation of ovarian tumors was used to point out the response of ovarian stromal cells to a specific marker. We followed both the ovarian tu-
mors in general and stromal ovarian tumors in particular and also the stromal reaction from the peritumoral area.

The main stromal reaction during a tumoral process is the stromal hyperplasia. Physiologically this is also increased with age. We choose to identify the stromal reaction in other types of ovarian tumors also, because we wanted to frame these changes in the global context of ovarian pathology. For struma ovarii ER was intense positive in stromal cell’s nucleus from the peritumoral ovarian tissue and was negative in thyroid tissue (epithelial cells and stroma also). For serous cystic adenomas ER was positive in epithelial cells, weakly positive and moderate positive in nuclei from adjacent ovarian stroma. There were also cases when ER was not positive at all inside the stroma (fig. 1, 2).

For mucinous adenocarcinoma ER was negative in tumoral stroma and nuclei of epithelial tumoral cells but positive in peritumoral ovarian stroma (fig. 3, 4).

![Fig. 1. ER (+) in epithelial cells, negative stroma](image1.png)

![Fig. 2. Weak focal and moderate ER (+) stroma](image2.png)

![Fig. 3. ER (-) in tumoral tissue](image3.png)

![Fig. 4. ER (+) in tumoral stroma](image4.png)

For ovarian fibrothecoma ER was focal positive in tumoral stroma and negative in adjacent ovarian stroma (fig. 5, 6).

PR immunohistochemical detections were done especially in the nuclei. PR concentration for all groups of study was similar. It was detected inside nuclei, cystic invaginations developed from the isolation of invaginated epithelium, metaplastic epithelium and ovarian stroma. PR concentration was not dependent to menopause instalation.

For mucinous ovarian adenocarcinoma, PR was focal positive in tumoral stroma and negative in tumoral epithelial cells; and also positive in nontumoral ovarian stroma.
Specific features of the stromal ovarian tumors

For cystic adenocarcinomas PR was negative in tumoral stroma and positive in nuclei of tumoral epithelial cells for one case and negative in tumor and focal weakly positive in stroma in the other case (fig. 7, 8, 9, 10).

For ovarian fibrothecoma PR was positive in different degrees inside tumoral stroma and also inside adjacent stromal tissue.

For the dosage of SMA inside struma ovarii was negative inside epithelial tumoral cells and positive in tumoral stroma. In the extratumoral stroma SMA was also positive, same as vascular walls and other smooth muscular fibers. For the mucinous ovarian adenocarcinoma SMA was positive...
in tumoral stroma and negative in epithelial tumoral cells. Inside normal stroma SMA is lightly positive, positive in vascular walls and other smooth muscular fibers. Fibrothecal tumoral cells were also intensely positive for SMA (fig. 11, 12, 13, 14).

Nuclear expression of S100 in different stages is correlated with the aggressiveness of an ovarian cancer, autocrine and paracrine conditions playing a main role in the determination of the aggressiveness of ovarian neoplastic cells. For the studied ovarian stroma S100 was negative in the selected cases, we had only cases with positive intern marker such as small amielinic nervous fibers (fig. 15, 16).
Caldesmon dosage revealed variable results and was positive mainly inside stromal ovarian tumors but also inside tumoral stroma and adjacent peritumoral stroma from other types of tumors (fig. 17, 18).

CONCLUSIONS
The increasement of stromal network installed with age determined the reduction of vascular support. The tumoral progression also induces the multiplication of the stromal network. Our study developed on two lots of patients pointed general epidemiologic parameters, statistic differences for clinical, paraclinical and anatomopathological diagnose for both categories.

We pointed a frequent positivity for ER inside the ovarian stroma, in all types of tumors not only for those with main stromal component. The figures we presented demonstrated the behavior of ovarian stroma for ER in general, for all groups of age.

We noticed the overexpression of estrogen and progesteron receptors in ovarian stroma from the ovaries with fields of stromal thecal hyperplasia both nodular and diffuse.

For the current medical practice we can suggest the utility of SMA dosage for certitude histological diagnosis of ovarian tumors. We did not remark the necessity of usage of S100 for the differentiation of ovarian tumors for both lots. The positivity of ovarian stroma for Caldesmon is obvious especially for stromal tumors. In this case we also noted the positivity of the adjacent stroma and vascular stromal elements. We also noted the negativity of this marker for epithelial components and epithelial originated tumors. To conclude, Caldesmon can be used for the diagnosis of ovarian stromal tumors.

REFERENCES


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**NEWS**

**ELAFIN-EXPRESSING BACTERIA, BENEFICIAL FOR INFLAMMATORY BOWEL DISEASE**

In a study by Motta *et al*, the intestinal mucosal expression of Elafin, a natural protease inhibitor, was determined in patients with inflammatory bowel disease. It was found that Elafin expression is diminished in those patients. Elafin has anti-inflammatory properties proved both *in vitro* and in animal models. Lactic acid bacteria were engineered to express and deliver Elafin to the inflammation site in colon. In mouse models of acute and chronic colitis, oral administration of lactic acid bacteria secreting Elafin decreased intestinal inflammation. In cultures of human intestinal epithelial cells treated with lactic acid bacteria expressing Elafin, the epithelium was protected from increased intestinal permeability and the release of cytokines or chemokines, which suggests that oral delivery of such bacteria could be useful in treatment of inflammatory bowel disease (Motta JP, Bermudez-Humaran LG, Deraison C et al. Food-Grade Bacteria Expressing Elafin Protect Against Inflammation and Restore Colon Homeostasis. *Science Translational Medicine* 2012; 4 (158): 158ra144 DOI: 10.1126/scitranslmed.3004212).