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## Expression of cancer-associated fibroblasts markers in epithelial ovarian neoplasms and its correlation with tumour progression, angiogenesis, and lymphangiogenesis: An immunohistochemical study

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**Background:** Tumours of the ovary are common forms of neoplasia in the female. The new histopathological, molecular and genetic studies provided the dualistic model of ovarian carcinogenesis: type I carcinoma with precursor lesions in the ovary forming part of a morphological and molecular continuum of adenoma-carcinoma sequence. They are confined to ovaries with the stable genome and without TP53 mutations. In type II carcinoma tumours develop de novo from tubal and/or ovarian surface epithelium, they are more aggressive, genetically unstable with TP53 mutations, and almost half cases show BRCA mutations. Tumour microenvironment (TME) acts as an important factor of tumorigenesis and development, once recruited, activated and accumulated to tumour area, these cells are called “cancer-associated fibroblasts”(CAFs). CAFs recognition depends on their morphology and specific biomarkers as SMA, vimentin, and FAP which is a cell surface glycoprotein expressed in stromal fibroblasts located in and around a tumour. The most common way of ovarian tumour metastasis is a direct extension to adjacent organs, besides spread through the lymphatic and vascular system.

**Aim:** The aim of the present work was to study the expression of CAF markers (FAP and SMA) in epithelial ovarian neoplasms and to correlate their expression with tumour progression, MVD using CD31 immunostaining and LVD using D2-40 immunostaining.

**Material and methods:** Sixty formalin fixed, paraffin-embedded samples of epithelial ovarian neoplasms were reevaluated. The diagnosis was as follows: 11 cases were benign, 8 borderline and 41 cases were malignant (of which 12 cases were type I and 29 cases were type II epithelial ovarian carcinoma). All tissue specimens were subjected to primary antibodies against FAP, SMA-alpha, D2-40 and CD 31 immunohistochemical staining.

**Results:** CAF expression: (detected by FAP and SMA immunohistochemistry) FAP was absent in most benign cases (81.8%) and present in all borderline cases the expression was weak in (87.5%) and strong in (12.5%) of borderline cases. In malignant cases, FAP was strongly expressed in (63.5%), moderate in (31.7) and weak in ( 4.9) of cases. SMA was absent in (54.5%) of benign cases and expressed in all borderline and malignant cases. In borderline cases, the expression was weak in (87.5%) and strong in (12.5%). In malignant cases, SMA expression was strong in (63.4%), moderate in (34.1) and weak in (2.4%) of cases. There was a statistically significant relation ( $P<0.05$ ) between tumour type and expression of SMA. There was a significant increased CAFs expression from borderline to type I epithelial ovarian carcinoma. Also, there was the difference in their expression within the malignant group itself according to its type. As regards stage there was a significant relation ( $P<0.01$ ) between tumour stage and presence of CAFs with increased expression in advanced stages. Assessment of MVD and LVD, as a measure of angiogenesis and lymphangiogenesis, using CD 31 and D2-40 respectively, and their correlation with CAFs showed that there was a significant increase in MVD and LVD from benign through borderline to type I epithelial ovarian carcinoma. Also, there was the difference in their expression from benign through borderline to the malignant epithelial tumour. Within the malignant group itself, both markers showed a significant difference between type I and type II ovarian carcinoma, confirming the difference in behavior and progression of each type. We found a significant relationship between tumour FIGO stage and LVD but no relation with MVD.

**Conclusions:** TME particularly CAFs provides a tumour architectural support and affects its physiology and function. CAFs play multiple roles in tumour development and progression. It is related to stage, metastasis, tumour type, LVD and MVD in human epithelial ovarian neoplasm. Their expression may be a poor prognostic indicator that indicates patients at great risk of developing metastasis.

**Notes:**

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