Correlation between cyclooxygenase-2 expression and cell proliferation in invasive ductal breast cancer

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Introduction: The study of lymphatic vessels and lymphatic-derived tumours is frequently complex, due to common characteristics of morphological features between blood and lymphatic endothelial cells, as well as to the lack of specific lymphatic endothelial markers. Prox-1, a homebox gene cloned by homology with the Drosophila gene prospero, that codifies a nuclear transcription factor that plays a major role during embryonic lymphangiogenesis and is supposed to be a useful marker to differentiate lymphatic from blood endothelial cells. Purpose: We studied a series of breast carcinomas in order to observe the specificity of this marker in lymphatic vessels. Methods: Tissue–array from formalin-fixed and paraffin-embedded samples of 116 invasive ductal carcinomas recovered from the Pathology files of IPATIMUP, Porto, Portugal were immunostained with a primary antibody raised against Prox-1 (diluted 1:133; Research Diagnostics, Inc., Flanders, NJ, USA). Results: Prox-1 immunostaining highlighted the lymphatic vessels, and was also detected in the cytoplasm and nuclei of neoplastic cells in 94.8% (110/116) of the cases. Conclusion: Our results suggest that invasive breast carcinoma cells can express Prox-1. Further studies are needed to understand the real meaning of this finding.

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UNUSUAL CYTOPLASMIC IMMUNOPOSITIVITY FOR MIB1 IN BREAST CARCINOMA

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INTRODUCTION:
Tumour cell proliferation can be assessed by a large number of antibodies: Ki-67, PCNA, KiS1… MIB1, the most commonly used, is a monoclonal antibody raised against the recombinant part of the Ki67 antigen. It reacts with cells in the late G1, S, G2 and M phases of the cell cycle and only stains nuclei with various intensity.
We report herein 2 cases of breast carcinoma with cytoplasmic immunoreactivity for MIB1.
POPULATION:
One occurred in a 62 year-old women, a 12 cm invasive ductal carcinoma, histoprognostic SBR grade 3. The second occurred in a 54 year-old women, a 23mm invasive ductal carcinoma, histoprognostic SBR grade 1. None of these patients received preoperative treatment.
Immunohistochemistry was done with MIB1 (Dako) after antigen retrieval (water bath) with LSAB kit and DAB revelation. The test was repeated at different times and with different blocks of the fixed tumour (Formaline, AFA) with the same results. The others immunohistochemistry (RE, RP, HER) didn't shown abnormal staining (nuclear staining for RE and RP, cytoplasmic staining for HER).
DISCUSSION:
In 1995, Hirokawa and al, first reported the cytoplasmic immunoreactivity for MIB1 in hyalinizing trabecular adenoma of the thyroid. Recently, two reports showed this unusual staining in atypical pleomorphic adenoma of the salivary gland and sclerosing haemangioma of the lung. To the best of our knowledge, this immunoreactivity hasn't been reported in breast tumours. Significance of this unusual staining is still unknown. There was no correlation between the properties of the cells stained and the mitotic count which suggests a cross-reaction of this immunostaining.
CONCLUSION:
Pathologists should be aware of this unusual MIB1 cytoplasmic staining. This pattern of reactivity of MIB1 in breast carcinoma may be a result of cross-reaction of the antibody.

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IGF-II MRNA EXPRESSION IN BREAST CANCER (BC) TISSUES AND CLINICAL OUTCOME.

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Insuline like growth factor II (IGF II) is an important regulator of neoplastic growth and it is generally expressed in stroma of BC tissues. Estrogen and Progesterone receptor (ER, PR) are considered a good prognostic predictors in BC. The aim of the study was to evaluate the impact of IGF II mRNA expression in clinical outcome in a large series of BC. The study group included 75 women (mean age +/- SD= 53.3+/-15.6 yr) submitted to radical mastectomy for ductal infiltrating breast carcinoma. The BC specimens was assessed for IGF II mRNA using in situ hybridization method and ER and PR by immunohistochemistry. Five years clinical follow-up was available in 65/79 BC (82.3%) and 46/65 (70.8%) were still alive and relapse free. ER+ was found in 39/65 (60%), PR + in 30/65 (46.2%) and stromal IGF II mRNA expression (IGF II +) in 33/65 (50.8%). 22/65 (33.8%) BC were IGF II+ ER+ and 19/65 (29.2%) IGF II+ PR+. No relationship was found between ER, PR, IGF II separately examined and clinical outcome. The better 5 yr survival was found in ER+ IGF II+ (16/22: 72.7%) and IGF II+ PR+ BC (14/19: 73.7%) and in contrast, the worse survival was found in IGF II+ ER- (6/11: 54.5%) and IGF II+ PR- (57.1%) groups. (p=0.006, p=0.02, respectively). These data indicate that stromal IGF II may be considered a new important predictive factor in BC and suggest that this growth factor may have a role in both differentiation or proliferation of BC cells

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CORRELATION BETWEEN CYCLOOXYGENASE-2 EXPRESSION AND CELL PROLIFERATION IN INVASIVE DUCTAL BREAST CANCER

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INTRODUCTION:Cyclooxigenase-2(COX-2)is overexpressed in breast cancer and may have a role in tumor development and progression.There has been inconsistency in the literature regarding the precise significance of this.Some studies have found no clinicopathological relevance at all, while others have concluded Cox-2 expression is an important biomarker in invasive disease, correlating with poor prognosis features.The aim of this study was to determine the relationships between Cox-2 expression and cell proliferation in breast cancer, and to correlate the expression of this enzyme with classic clinicopathological parameters.
MATERIAL AND METHODS:We retrospectively analyzed 150 breast tumors in paraffin embeded tissue and from medical records, obtained clinicopathological data.Regarding to tumor grade we had three groups of patients and each group consisted of 50 patients.Cox-2 expression was investigated by immunohistochemistry using monoclonal antibody. Immunohistochemistry was done following protocol on DAKO TechMate Horizon automated immunostainer.S-phase fraction (SPF)determined by flow cytometry used as a marker of cell proliferation.
RESULTS:Cox-2 expression was detected in 86%of all tumors studied.The preliminary results have shown that Cox-2 protein expression significantly correlates only with tumor

grade but not with SPF.We have found statistically significant difference in expression of Cox-2 in different grade of tumors (p=0.02).Comparing different grade with SPF we found statistically significant higher SPF in poorly differentiated tumors (p<0.001).
CONCLUSIONS:We have confirmed that Cox-2 expression does occur in invasive breast ductal cancer and is associated with tumor grade.It remains to be investigated whether treatment with selective inhibitors of Cox-2 may be an additional therapeutic option for patients with breast cancer.

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IMMUNOHISTOCHEMICAL ANALYSIS OF RET AND ITS LIGAND GDNF IN 139 CASES OF BREAST CANCER

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Introduction: The RET proto-oncogene tyrosine kinase receptor is activated by a ligand complex comprising glial cell line-derived neurotrophic factor (GDNF) and GDNF family receptor alpha1 (GFRalpha1). They are expressed in multiple organs during development and in some types of human tumors in adults. In this study we evaluated the expression of RET, and GDNF in different types of breast cancer.
Material and Methods: RET, expression was analyzed in samples of formalin-fixed tissues from tumoral zone, from 139 patients with different types of breast cancer: 109 IDC; 5 IC; 7 ILC; 6 mucinous carcimomas; 4 medullary carcinomas; 3 papillary carcinomas 2 tubular carcinomas and others (3) using immunohistochemical methods.
Results: A total of 98/137 (71,6%) of breast tumors showed citoplasmic immunoreactivity for RET, and 130/138 (71,6%) for GDNF. By statistical analysis based on 111 months follow up showed that RET expression was associated with less tendency to the regional lymph nodes metastases (p<0,0001); less tendency to relapse (p<0,004); increase of overall survival (p<0,0004); There was no statistically significant correlation of RET or GDNF expression with the histological grade, microscopic type, size or stage. Those findings were not supported by multivariant analysis.
Conclusions: We found that RET and its GDNF/GFRalpha1 ligand complex were expressed in normal breast tissues and in a high percentage of different types of breast tumors using immunohistochemical methods. The presence of RET did not show clear association with any particular light microscopic growth pattern or special tumor subtype, but interestingly, this expression was associated with less tendency to the lymph nodes metastases and increase of overall survival. In summary RET determination by immunohistochemical analysis could be used as a prognostic factor in breast cancer.

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PROGNOSTIC VALUE OF MIB1 PROLIFERATION INDEX AND C-ERBB2 IN PATIENTS WITH STAGE II BREAST CANCER AND LYMPH NODE INVOLVEMENT

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INTRODUCTION: Breast cancer is the first leading cause of cancer in women from Spain, and its incidente rates have increased in the recent last years. Study of prognostic value of different factors in breast cancer patients with lymph node involvement can identify subgroups of patients with high risk for more effective clinical management. C-erbB2 that encodes HER2/ Neu protein (p185HER2), and MIB1 proliferation index are useful parameters to assess this issue.
PURPOSE: The goal of this study was to evaluate if the prognostic role of c-erbB2 and MIB-1 proliferation index, p53, S-phase, were dependent or independently useful to characterise more aggressive breast tumors.
PATIENTS AND METHODS: 87 positive-node infiltrating breast cancer patients classified as stage II (T2N1). C-erbB2, p53, MIB-1 proliferation index, estrogen (ER) and progesteron receptors (PR) were determined immunohistochemically by assigning a score with an analysis image software. C-erbB2 membrane expression was graded negative, indeterminate, 1+, 2+, 3+ when ¡Ý5%, 20%-30%, 30%-50%, and more than 50% of cells were stained, respectively. Comparisons in distributions were analyzed by ANOVA and Pearson tests, using SPSS. Differences in disease-free and overall survival were evaluated by using the log-rank test.
RESULTS: 48.3% of the patients resulted to be negative for c-erbB2, whereas 12.6%, 18.4%, 15% and 5.7% of the patients were indeterminate, 1+, 2+ and 3+, respectively. C-erbB2 immunostaining was correlated to node involvement and number of positive nodes (P= 0.022, P=0.023, respectively), tumor size (P= 0.037) and PR (P=0.03). There are no correlations between c-erbB2 immunostaining, age, ploidy, MIB-1 and ER. The median follow-up time was 90 months. Disease-free survival is inversely correlated to c-erbB2 immunostaining (P= 0.027), number of positive nodes (P=0.037) and tumor size (P=0.042), being nearly significant for MIB1 (p=0.09). Predictive value for c-erbB2 was confirmed with a relative risk of 2.5 times in multivariate analysis.
CONCLUSIONS: 1. Higher proliferation index is a bad prognosis factor in patients with infiltrating breast cancer patients, stage II tumors and lymph node involvement. 2. C-erbB2 oncogene is an indicator of bad prognosis in these patients. 3. Patients that were negative for proliferation index and C-erb-B2 presented longer overall survival.

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PLATELET-DERIVED GROWTH FACTOR RECEPTOR-ALPHA (PDGFR-ALPHA) EXPRESSION IN INVASIVE BREAST CARCINOMAS

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Introduction: Receptor tyrosine kinases have been extensively studied due to their frequently abnormal activation in the development and progression of many human cancers. Platelet-derived growth factor receptors (PDGFRs) are receptors with intrinsic tyrosine kinase activity that regulate several functions in normal cells and are widely expressed in a variety of malignancies. After the demonstration that GISTs without c-kit mutations harbour PDGFR-alpha activating mutations, and that it is also a therapeutic target for imatinib mesylate, the interest for this receptor increased considerably. Since breast cancer is one of the most frequent neoplasia in women worldwide, and there are only one study reporting PDGFR-alpha expression in breast carcinomas, the aim of this work was to investigate the potential meaning of PDGFR-alpha expression in invasive mammary carcinomas.