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PERIDUCTAL MASTITIS AND MAMMARY DUCT ECTASIA- TWO STAGES OF THE SAME DISEASE?

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This paper deals with a disease known under several names: obliterative mastitis, plasma cell mastitis, periductal mastitis, comedomastitis, mammary duct ectasia, which seem to define different stages of the same illness.

Out of 67 cases of benign breast diseases recorded in our hospital during a 3-year interval, 15 cases were diagnosed as periductal mastitis or mammary duct ectasia.

The dominant pathological findings in younger patients (17-40 years) were periductal infiltration with plasma cells, lymphocytes or polymorphic cells, while in older patients (over 52) duct ectasia and nipple retraction were prevalent, being frequently associated with periductal infiltration. Microbiological examination of the intraoperative samples showed different germs in most cases. Thus antibiotic prophylaxis was justified in our cases.

Our study supports the idea that this disease begins with a silent ductal infection with periductal infiltration, and ends with chronic inflammation and fibrosis with consequent duct ectasia. Therefore, periductal mastitis, non-puerperal mastitis and duct ectasia are stages of the same pathological process. Due to the clinical similarity with breast cancer, treatment by sectorectomy becomes mandatory.

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MRP AND *MDR1* GENE EXPRESSION IN PRIMARY BREAST CARCINOMAS

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To assess the clinically important mechanisms of drug resistance in breast cancer, we determined the expression of the *MRP* and *MDR1* genes in primary breast carcinoma specimens. Using RT-PCR, *MRP* RNA was detected in all specimens and *MDR1* RNA in only 49 (51%) of the samples (n=97). Immunohistochemistry on frozen sections (n=30) was performed with monoclonal antibodies QCRL-1 and QCRL-3 (provided by Dr. S. Cole, Kingston) and C219, respectively. MRP staining was strong in 7 (23%) and weak in the remaining 23 (77%) specimens. Strong staining was more frequently observed in T3 & T4 tumors than in T1 & T2 tumors, was present in the primary tumors of all 3 patients with distant metastases but was independent of histologic grade, estrogen receptor status and lymph node involvement. P-glycoprotein expression was seen in 15 (50%) specimens. Thus both the *MRP* and the *MDR1* genes are frequently expressed in breast cancer and might be involved in the clinical drug resistance of this disease.

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STUDY ON SENTINEL NODES IN BREAST CANCER USING LYMPHOSCINTIGRAPHY AND RADIO-GUIDED PROBE.

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This is an ongoing study involving all patients at our Institute who undergo breast surgery and total axillary dissection. The objectives are: (1) to identify the sentinel node or first node that receives lymph from the tumour area by lymphoscintigraphy following injection of 99mTc-labeled human albumin into the skin overlying the tumour; (2) to mark the sentinel node thus identified by means of an indelible sign on the skin over the node; (3) to determine the feasibility of isolating this node surgically with the aid of a radio-guided probe; and (4) to verify how often the node thus isolated is metastatic in comparison with involvement of the other removed nodes.
The highly sensitive probe permits location of the radioactive node within adipose tissue: our initial experience is that this node is found within a few minutes of opening the axilla. The sentinel node is removed and tagged separately from all the other nodes.
Since January 1996, 16 consecutive cases have been studied. Histological examination has revealed 6 positive sentinel nodes plus other nodes involved, 2 positive sentinel nodes with the other nodes negative and 8 negative sentinel nodes with all other nodes negative. If a negative sentinel node is found to correlate reliably with a completely negative axilla, this will probably allow reduced extent of axillary dissection in future cases of negative sentinel node.

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PACLITAXEL CONTAINING HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS BLOOD STEM CELL SUPPORT FOR HIGH RISK PRIMARY BREAST CANCER

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In this phase II study a new high-dose regimen was investigated as consolidation after standard-dose adjuvant chemotherapy of primary breast cancer involving 10 or more axillary lymph nodes. Ten patients with a mean age of 45 years and a mean of 14 positive axillary lymph nodes after mastectomy (n=8) or segmentectomy (n=2) received two cycles of cyclophosphamide (CY), doxorubicin, and fluorouracil (CAF) within 56 days of surgery. Then, autologous peripheral blood stem cells (APBSC) were mobilized with CY and granulocyte colony-stimulating factor (G-CSF) and enriched for CD34+ cells with immunoadsorption. Thereby, 53% of initial CD34+ cells were recovered and a mean purity of 77% was achieved. High-dose chemotherapy consisted of paclitaxel, carboplatin, and CY followed by infusion of a mean of 5.1 x 10^6 CD34+/kg b.w.G-CSF was given as continuous infusion starting one day after APBSC transfusion until neutrophil recovery. Main toxicity of the new high-dose regimen consisted of diarrhea WHO grade 1 to 3 (n=5), peripheral neuropathy WHO grade 1 (n=4) and transient elevation of liver enzymes (n=3). All patients experienced rapid and sustained hematologic recovery and are in excellent performance status 1 to 22 (mean 9) months after APBSC transfusion. In conclusion, paclitaxel in combination with carboplatin and cyclophosphamide is a well tolerated high-dose chemotherapy with acceptable toxicity. Evaluation of relapse rates in patients with high-risk primary breast cancer compared with reported high-dose regimens has to await longer observation times and randomized studies.

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PREOPERATIVE, NEOADJUVANT CHEMOTHERAPY LEADS TO BREAST CONSERVING SURGERY IN LOCALLY ADVANCED BREAST CANCER

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Conservation of the breast is one of the major goals of modern breast cancer surgery. Very large tumors (T3/T4) or those with unfavorable localization remained subject to mastectomy until recently. Thus, we evaluated the impact of preoperative chemotherapy on the reduction of tumor size and the subsequent possibility of breast conserving surgery in patients with locally advanced breast cancer. We report on 48 patients suffering from biopsy proven breast cancer, who would have been treated with mastectomy when conventional criteria would have been applied. These patients were treated with preoperative cytotoxic chemotherapy using the CMF or FEC regimen. Study end points were clinical and pathological response rates and the surgical method which could be applied at the end of the preoperative treatment. Overall in 41 out of 48 patients (85%), we observed an objective response 6 patients (13%) had a complete pathological response at the time of their operation and 35 patients (73%) experienced a partial response (i.e. > 50% shrinkage of tumor). 7 patients had stable disease and no patient progressed during the preoperative therapy period. 33 patients (69%) could have a breast conserving procedure, and only 15 (31%) had to undergo mastectomy. Thus, preoperative chemotherapy appears to be a valuable tool in the treatment of large breast cancers in order to allow breast conserving surgery in a substantial number of patients with T3/T4-tumors. It remains to be determined, whether the neoadjuvant treatment approach to breast cancer leads also to a reduced relapse rate or a prolongation of survival.

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ELEVATED VASCULAR ENDOTHELIAL GROWTH FACTOR IN BREAST CANCER

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The source of tumour derived VEGF and the mechanism of its release have not been fully clarified. We hypothesized that tumour associated macrophages are a source of tumour VEGF. Blood samples were collected from patients with benign fibroadenoma (n=13) and breast carcinoma (n=13) pre-operatively and the serum assayed for VEGF by capture ELISA. Statistical analysis was performed using Students t test. Data is expressed as mean ± standard deviation. Serum VEGF in patients with malignant breast disease was significantly elevated (6.35±3.79 pg VEGF/mg serum protein; p=0.02) compared to patients with benign fibroadenoma (1.64±1.65 pg VEGF/mg serum protein). To simulate the tumour environment, human peripheral blood monocytes were cultured *in vitro* for 72hrs, activated with IFNg and incubated under hypoxic conditions with breast tumour cell conditioned media. Culture supernatants were assayed for VEGF by ELISA. Statistical analysis was performed using ANOVA with Bonferroni correction. Data is expressed as mean ± standard deviation. Monocyte derived macrophages (mdms) cultured in tumour conditioned medium under hypoxic conditions produced significantly higher amounts of VEGF (39.97 ± 10.560 pg VEGF/ μg cell protein; p=0.002) compared to controls (0.20 ± 0.088 pg VEGF/ μg cell protein). This study demonstrates elevated circulating levels of VEGF in patients with malignant breast disease and shows that breast tumour cells produce a soluble factor which stimulates macrophage production of VEGF under hypoxic conditions.