Abstract. Male breast carcinoma is a rare neoplasm, accounting for fewer than 1% of all malignancies of the breast. We report the case of a 65-year-old man who presented at our institution with a lump in his left breast. Histologically, the tumour had marked nuclear pleomorphism and contained multinucleated giant cells. Immunohistochemical staining demonstrated that the tumour cells were positive for cytokeratin AE1/AE3, E-cadherin, p53, Ki-67, cyclin D1, estrogen and progesterone receptor proteins, but negative for c-ERB-B2 and CD68. Based on the latest World Health Organization classification, the tumour was diagnosed as pleomorphic ductal carcinoma of the breast. To the Authors' knowledge, this is the first case report of pleomorphic carcinoma of male breast.

Pleomorphic Ductal Carcinoma of the Male Breast: Report of a Rare Case and Review of Literature

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Key Words: Male breast, ductal pleomorphic carcinoma, histopathology, immunohistochemistry.

Case Report

A 65-year-old male presented with a painless subareolar mass in the left breast, of 4 months duration. The mass had gradually increased in size. During physical examination, inspection of the breast did not show any volume or skin alteration such as retraction. A firm and well-circumscribed mass was palpable in the subareolar region of the left breast. There was no nipple discharge. No pathological lymph nodes were palpable in the axilla or in the supraclavicular region. Right breast examination was completely normal. Mammography showed a mass in the subareolar portion of the left breast. A core biopsy with a Tru-cut device was performed, resulting in a pathological report of invasive carcinoma, grade 3. Surgical excision was recommended. During surgery, sentinel node biopsy was performed, and intraoperative histopathological examination by means of the technique routinely used at our Institute, with 60 sections for each node, showed the presence of a macrometastasis. Complete axillary lymph node dissection was therefore performed. Three days after surgery, the patient was discharged, in very good condition.

On gross examination, the mastectomy specimen measured 11x7x5 cm. The cut surface showed a well-circumscribed solid mass measuring 2.5x2 cm in size. Representative samples were fixed in 10% formalin, dehydrated and embedded in paraffin. Sections were stained with haematoxylin and eosin. In addition, immunohistochemical studies were performed with peroxidase-antiperoxidase technique using antibodies to oestrogen receptor protein, progesterone receptor protein, E-cadherin, cyclin D1, BCL-2, c-ERB-B2 protein, p53, and Ki-67, cytokeratin AE1/AE3, synaptophysin, chromogranin and CD68 (all from DAKO Copenhagen Denmark).

The tumour was histological grade III and, by definition, contained pleomorphic tumour cells with more than 6-fold variation in nuclear size, in more than 50% of the tumour cells evaluated. There were numerous tumour giant cells containing two or more nuclei with heterogeneous size and prominent nucleoli (Figures 1 and 2). Focal areas of tumour
necrosis were also present. Mitoses were frequent (20 mitoses per 10 high-power fields) and some were atypical. The nipple was free from tumour infiltration. Three out of 16 dissected lymph nodes were tumour positive, including the sentinel node. Based on the above findings, a final diagnosis of pleomorphic carcinoma of the breast was made. The disease in this patient was staged as pT2 N1aMx.

Tumour cells showed high hormone receptor positivity for both oestrogen and progesterone, but were negative for c-ERB-B2. The tumour was diffusely positive for cytokeratin AE1/AE3 and E-cadherin. Immunostaining for synaptophysin, chromogranin and CD68 produced negative results. Heterogeneous cytoplasmic staining for BCL-2 was observed (Figure 2). Ki-67, p53 and cyclin D1 positivity was found in 40%, 35% and 30% of tumour cells, respectively.

Discussion

We present a rare case of pleomorphic giant cell carcinoma of the male breast. More than 50% of the tumour cells had large nuclei, indicative of higher DNA content, and numerous tumour cells characteristically exhibited a multinuclear phenotype. Pleomorphic carcinoma has been previously described in many organs, most frequently in the lung, but rarely also in the breast, pancreas, intestine, kidney, liver, urinary bladder, gall bladder, thyroid, stomach and prostate (6). To the best of our knowledge, primary pleomorphic giant cell carcinoma of the male breast has not been recognized or previously described in the literature.

Pleomorphic tumour cells can be present in other breast tumours, such as invasive pleomorphic lobular carcinoma, carcinoma with osteoclastic giant cells, mammary sarcoma, and metastatic tumours (6). Metastasis of carcinoma in the breast is a rare event and usually is multicentric. Careful examination of tumour morphology with the help of immunohistochemical studies should lead to a correct diagnosis. Invasive pleomorphic lobular carcinoma is a distinctive, aggressive subtype of invasive lobular carcinoma (7). Similar to pleomorphic carcinoma, it exhibits enlarged nuclei with hyperchromasia, irregularities, and marked pleomorphism. However, a growth pattern typical of classic invasive lobular carcinoma with linear arrays of tumour cells, often in a targetoid distribution, and lack of E-cadherin expression are the most prominent features that separate these tumours from ductal neoplasms (8). Due to the presence of multinucleated tumour cells, pleomorphic carcinoma can also be misdiagnosed as mammary carcinoma with osteoclast-like giant cells (9-10). This entity is characterized by a population of multinucleated osteoclast-like giant cells in a fibroblastic or vascularized stroma separating nests and cords of invasive or intraductal carcinoma. In mammary carcinoma with osteoclastic-like giant cells, giant cells have cytologically bland, monomorphic nuclei and are invariably non-reactive for epithelial markers (10). Multinucleated giant cells in the present case had large, hyperchromatic and irregular nuclei, and prominent nucleoli. They also showed positivity for epithelial markers and were not immunoreactive for CD68.

Mutation and overexpression frequencies of the tumour suppressor gene p53 are both around 20-40% in conventional breast cancer (11), whereas BCL-2 expression is inversely related to WHO tumour grade (12). p53, which mediates G1 arrest and apoptosis, is subject to many mutations, leading

Figure 1. Pleomorphic ductal breast carcinoma showing sheets and cords of polygonal epithelioid atypical cells, with marked pleomorphism and multinucleation. H&E x100.

Figure 2. BCL-2 protein is heterogeneously expressed by tumour cells. Note weak, focal cytoplasmic staining for BCL-2 in multinucleated tumour cells (×400).
to prolonged half-life and detectable accumulation of the p53 protein (13). Loss of p53 function eliminates the G1 checkpoint, leading to replication in the presence of chromosomal alterations. The end result is increased proliferation and genomic instability, leading to accumulation of other genetic defects contributing to neoplastic transformation and progression (13). Immunohistochemical staining of p53 suffers from both false-negative and false-positive results, compared with p53 gene sequencing, so the introduction of additional parameters in analyses can be expected to increase precision.

In our immunohistochemical analysis, Ki-67 and cyclin D1 overexpression was found. Ki-67 is a nuclear antigen expressed in the G1, S and G2 phases, but not in G0 or the resting phase of the cell cycle. It has become established as a proliferation marker in breast cancer (14). Overexpression of cyclin D1 is often found in many different tumour types, e.g. breast carcinoma and squamous cell carcinoma of the head and neck (15). Accumulation of cyclin D1 in invasive carcinoma is associated with deregulation of the PRB pathway of cell cycle control (16-17). Hence, overexpression of p53, cyclin D1, and Ki-67 suggests cell cycle control disturbances in our case of pleomorphic breast carcinoma.

Cases of giant cell carcinomas have been associated with rapid tumour dissemination and a poor prognosis (6). In contrast, long-term survival of up to 11 years has been recorded (18). There is increasing evidence that the mere presence of tumour giant cells in lung carcinoma does not, in itself, indicate a more aggressive tumour type (18). Therefore, the prognostic importance of a tumour giant cell component, with or without more differentiated epithelial elements, remains unclear.

In conclusion, we have presented a rare case of pleomorphic carcinoma of the male breast, characterized by aberrant expression of cell cycle proteins (p53, cyclin D1 and Ki-67). Such morphological and immunohistochemical findings may be considered as the extreme grade of the dedifferentiation process in this unusual variant of breast carcinoma.

References


Received May 12, 2011
Revised July 12, 2011
Accepted July 13, 2011