Lobular Breast Cancer in a Male Patient with a Previous History of Irradiation Due to Hodgkin’s Disease

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Male breast cancer · Histology · Immunohistochemistry · Pathology

\section*{Introduction}

Male breast cancer accounts for less than 1\% of all breast cancers and less than 1\% of all male cancer deaths [1]. Due to the fact that the male breast most often does not consist of lobules and acini, lobular carcinoma of the male breast is exceptionally rare [2]. Approximately 20 cases have been reported so far all of which were of the classical subtype (table 1) [3–18], with the exception of 1 case which showed a histological picture of pleomorphic lobular cancer [19]. In this article, we present a male patient with the alveolar variant of lobular cancer, proved immunohistochemically by an E-cadherin-negative result.

\section*{Case Report}

A 56-year-old male patient was admitted with changes to the central quadrant of the right breast, which he had noticed 1 month earlier. He was married with 2 healthy children, and worked as a manager in a primary school. The patient did not report any trauma, liver disorders, gynecomastia, or use of hormones and other drugs. However, he had suffered from Hodgkin’s lymphoma, a type of nodular sclerosis, 14 years ago. The disease had reached the second clinical stage, and was localized in the right supraclavicular and cervical lymph nodes. The treatment had consisted of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) chemotherapy and radiotherapy, after which a complete remission was achieved. To this day the patient has remained relapse-free as verified by hematology reports from regular control examinations.

During clinical examination the presence of a firm, painless, mobile, subareolar tumor mass the size of a small nut was noted in the central quadrant of the right breast, with no retraction of the skin. Axillary lymph nodes were not palpable. On ultrasound examination the lesion measured 22 mm in diameter, had unclear boundaries, and showed pathological
vascularization zones and distal weakness of the ultrasound signal. Oncologists staged the tumor as T2N0M0 and recommended surgical treatment. After excision of the tumor and intraoperative frozen section histological analysis, a malignant process was confirmed and mastectomy and axillary lymph node dissection performed. A total of 14 lymph nodes were examined, and none revealed metastatic deposits. No complications were observed in the postoperative period, and after 5 days the patient was discharged from hospital in good condition. Further treatment consisted of radiation therapy and chemotherapy in 6 cycles according to the FAC protocol (cyclophosphamide, adriamycin, 5-fluorouracil), and tamoxifen (20 mg daily). 2 years after the surgery, the patient is alive without any residual or metastatic disease.

Pathohistological Findings

Analysis of tumor tissue included a sample of yellowish color and irregular shape, measuring 42 mm in diameter. Cross section showed a white-yellowish change with circumscribed edges and of firm consistency, measuring 21 × 18 mm. Several samples were taken of which 2 were prepared at cryostatic condition for ex tempore analysis; others were fixed for 24 h in 4% formaldehyde and paraffin-embedded. Paraffin blocks were cut into 5-μm sections, stained with hematoxylin and eosin, and immunohistochemically analyzed at a later stage. Microscopically the tumor showed the histological picture of an alveolar variant of lobular carcinoma with relatively uniform cells (fig. 1 a), light cytoplasm, regular round nuclei, cell nests and alveolar arrangements, desmoplastic reaction, and scarce lymphocytic infiltration. An in situ component was present. Immunohistochemically the tumor cells showed strong positivity (score 8) for estrogen receptors (fig. 1 b), weak-to-moderate positivity (score 4–5) for progesterone receptors (fig. 1 c), and negativity for Her-2 receptors (fig. 1 d). The cytoplasmic membrane did not stain for E-cadherin (figs. 1 e and f), and the Ki-67 proliferation index was very low (2%).

Discussion

Male breast cancer is extremely rare (less than 1% of all breast cancers) and usually appears at an older age (> 60 years). The most frequent histology types are ductal invasive carcinoma (around 93%) and papillary carcinoma (3%) [2]. In a large series from France investigating male breast cancer (397 cases from different regional centers, 1970–1992), ductal invasive carcinoma was present in 97%, while other cases

**Table 1.** Review of cases of lobular male breast cancer in the literature

<table>
<thead>
<tr>
<th>Authors [ref.]</th>
<th>Year</th>
<th>Cases, n</th>
<th>Age, years</th>
<th>Side</th>
<th>Lobular carcinoma (subtype)</th>
<th>TNM status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norris et al. [3]</td>
<td>1969</td>
<td>1</td>
<td></td>
<td>unknown</td>
<td>small cell carcinoma</td>
<td>unknown</td>
</tr>
<tr>
<td>Yogore and Sahgal [5]</td>
<td>1977</td>
<td>1</td>
<td>56</td>
<td>left</td>
<td>small cell carcinoma</td>
<td>T2NoMo</td>
</tr>
<tr>
<td>Sanchez et al. [6]</td>
<td>1986</td>
<td>1</td>
<td>61</td>
<td>left and right</td>
<td>classic subtype</td>
<td>unknown</td>
</tr>
<tr>
<td>Nance and Reddick [7]</td>
<td>1989</td>
<td>1</td>
<td>82</td>
<td>right</td>
<td>classic subtype</td>
<td>TxNoMx</td>
</tr>
<tr>
<td>Sawabe et al. [8]</td>
<td>1992</td>
<td>1</td>
<td>74</td>
<td>unknown</td>
<td>classic subtype</td>
<td>unknown</td>
</tr>
<tr>
<td>Michaels et al. [9]</td>
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<td>1</td>
<td>59</td>
<td>right</td>
<td>classic subtype</td>
<td>TxNoM0</td>
</tr>
<tr>
<td>Yamamoto et al. [10]</td>
<td>1997</td>
<td>1</td>
<td>68</td>
<td>left</td>
<td>classic subtype</td>
<td>T4NxM1</td>
</tr>
<tr>
<td>San Miguel et al. [11]</td>
<td>1997</td>
<td>1</td>
<td>62</td>
<td>left</td>
<td>classic subtype</td>
<td>unknown</td>
</tr>
<tr>
<td>Scheidbach et al. [12]</td>
<td>2000</td>
<td>1</td>
<td>85</td>
<td>right</td>
<td>classic subtype</td>
<td>T4N2Mo</td>
</tr>
<tr>
<td>Koc et al. [13]</td>
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<td>1</td>
<td>52</td>
<td>right</td>
<td>classic subtype</td>
<td>T2NoMo</td>
</tr>
<tr>
<td>Chandrasekharan et al. [14]</td>
<td>2001</td>
<td>2</td>
<td>53/73</td>
<td>left/right</td>
<td>pleomorphic subtype/classic subtype</td>
<td>T2N1M0/T2N1Mo</td>
</tr>
<tr>
<td>Malý et al. [19]</td>
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<td>1</td>
<td>44</td>
<td>left</td>
<td>pleomorphic subtype</td>
<td>T2NoMo</td>
</tr>
<tr>
<td>Mardi and Sharma [15]</td>
<td>2006</td>
<td>1</td>
<td>56</td>
<td>left</td>
<td>classic subtype</td>
<td>unknown</td>
</tr>
<tr>
<td>Erhan et al. [16]</td>
<td>2006</td>
<td>1</td>
<td>64</td>
<td>left</td>
<td>classic subtype</td>
<td>T2NoM0</td>
</tr>
<tr>
<td>Spencer and Shutter [17]</td>
<td>2008</td>
<td>1</td>
<td>58</td>
<td>left and right</td>
<td>classic subtype</td>
<td>T4NXM1</td>
</tr>
<tr>
<td>Burga et al. [18]</td>
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<td>1</td>
<td>?</td>
<td>unknown</td>
<td>unknown</td>
<td>unknown</td>
</tr>
</tbody>
</table>

**Fig. 1.** a Invasive lobular carcinoma, alveolar subtype (hematoxylin and eosin stain; original magnification ×100). b Tumor cells were strongly positive (score 8) for estrogen receptor (ER immunostaining with hematoxylin counterstain, original magnification ×100). c Tumor cells were weak-to-moderately positive (score 4–5) for progesterone receptor (PR immunostaining with hematoxylin counterstain, original magnification ×200). d Tumor cells were negative for Her-2 receptors (Her-2 immunostaining with hematoxylin counterstain, original magnification ×200). e Complete loss of E-cadherin expression in lobular cancer cells (E-cadherin immunostaining with hematoxylin counterstain, original magnification ×200). f Myoepithelial cells were positive for E-cadherin in foci of lobular in situ carcinoma (E-cadherin immunostaining with hematoxylin counterstain, original magnification ×400).
represented in situ changes [20]. Burga et al. [18] in their study of 759 archived cases of primary invasive carcinoma involving the male breast, revealed that 84.7% were pure infiltrating ductal carcinoma and 0.4% pure lobular carcinoma.

Analysis of the histological features of male breast cancer as compared to female breast cancer indicates the presence of only 1 difference: lobular (also known as small-cell) cancer is extremely rare in men due to hormonal factors and the lack of acini and lobules [3–5]. However, although true lobule formation is not usually present, lobules are sometimes seen, but there is disagreement as to whether this feature occurs only in cases with a known endocrine etiology [20–22].

Some studies have compared the stages of breast cancer in male patients with those in female patients, indicating that there was no significant difference in survival time and clinical course [23, 24]. In contrast the results of other studies showed that male breast cancers can be more aggressive and have a worse prognosis [25, 26]. Scarcity of breast tissue, small distance between the skin and the areola, richness in dermal lymphatic vessels, early regional and distant metastasis, and late diagnosis probably are reasons for this [27]. Particularly the poorer prognosis of male patients is primarily connected to the disease being diagnosed at a later stage compared to women, at which stage lymph node involvement is found in more that 60% of the patients [28].

In our patient, the tumor cells showed estrogen and progesterone receptor positivity. Studies show that although most male breast cancers are estrogen-positive, they have no prognostic advantage compared to women [29], and the reason for this is thought to be the commonly higher clinic disease stage in male patients [30]. Furthermore, male breast cancers show much less p53 positivity and overexpression of Her-2 receptors [31]. Immunohistochemical staining for E-cadherin helps in differentiating the histology of male breast cancers; moderate to intense membrane expression is present in 85% of ductal cancers, while the lobular variant shows total negativity for E-cadherin [32–34]. All reported cases of lobular carcinoma of the male breast have met the established histomorphological criteria, with the exception of the pleomorphic variant which demonstrates negative immunohistochemical staining for E-cadherin [19].

Overall male breast cancer has a low incidence, and hence its etiopathogenesis, immunophenotype, and clinical course have been much less investigated than female breast cancer. Numerous studies have confirmed clear genetic differences so that the poorer prognosis may be related to a lesser efficacy of available therapies irrespective of the differences in the biological profile of male and female breast cancer [35, 36]. Numerous factors are associated with higher risk in male breast cancer. The most frequently reported are family history of breast cancer [37] and genetic factors [38]. Eldar et al. [39] described 10 cases of breast cancer appearing after chest irradiation. Other suggested contributing factors are Klinefelter’s syndrome [6, 14], gynecomastia, obesity, clinical conditions causing hypogonadism (testicular trauma and infertility), and liver diseases causing hyperestrogenism [38]. Together with endocrine disorders, long-lasting use of certain drugs can cause proliferation of lobular structures, which is the main predisposing factor for the lobular variant of male breast cancer [11].

Our patient is a phenotypically and genotypically proven male, with no use of drugs with estrogen activity (e.g., hormone therapy, cimetidine) or intrinsic conditions causing a hyperestrogenic state (cirrhosis or other liver diseases). His family history did not include malign breast diseases in either female or male relatives. Prior to Hodgkin’s disease, which was treated with cytotoxic agents and radiation therapy, the patient had been completely healthy. Therefore, the only risk factor that could be responsible for the appearance of this extremely rare male disease is radiation therapy for previous disease. According to the literature and our findings, this is the first presentation of an alveolar variant of lobular male breast cancer with negative staining for E-cadherin.

**Disclosure Statement**

The authors declare that they do not have competing interests.

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**References**


