A Rare Case of Invasive Breast Lobular Carcinoma Overexpressing Her2

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Abstract

Invasive lobular carcinoma (ILC) appears to have distinctive clinical and biologic characteristics compared with Invasive ductal carcinoma (IDC), as the overexpression of HER2.

The association of HER2 positive phenotype with classical ILC is very rare, therefore we present an atypical case of classical ILC overexpressing HER2 in immunohistochemical study (Hercept test HER2 3+).

We describe the case, and propose a literature review of HER2 phenotype positive in ILC breast cancer.

Introduction

Lobular carcinoma of the breast was first described by Foote and Stewart in 1941[1-2]; invasive lobular carcinoma (ILC) comprises approximately 10% of breast cancers, the variation in reported incidence (0.6-20%) [3-4] is most probably due to different histopathological criteria used to define ILC rather than a real variation in incidence. Classical ILC, by definition, is a low-grade tumour with little or no nuclear atypia and a low mitotic rate.

Because it is less common than Infiltrating ductal carcinoma (IDC), knowledge about the clinical outcome of lobular carcinoma has been based on studies including relatively small numbers of patients. In the few reported data, ILC appears to have distinctive clinical and biologic characteristics compared with IDC; one of those differences is the epidermal growth factor receptor HER2.

HER2neu is a proto-oncogene located on the long arm of chromosome 17 [5], low levels of the protein expressed by this gene are normally present in many adult tissues including breast, endometrium, prostate and ovary. Amplification of this gene and increased levels of the protein product have been found in between 10 and 35% of invasive breast carcinomas [6-8].

Studies have shown that HER2 positive (overexpression or amplification) is a poor prognostic factor for patients with both axillary lymph node-negative and positive breast cancer [9-11]. Therefore determining HER2 status is primordial of patients to precise the prognostic. Assay results independently guide therapeutic decisions regarding the suitability of Trastuzumab treatment for both metastatic and adjuvant setting [12]. Trials demonstrated that the addition of Trastuzumab, administered with chemotherapy resulted in a significant increase of overall survival when compared with chemotherapy alone for patients with HER2 positive, reducing the risk of recurrence and mortality by one half and one third, respectively for early-stage breast cancers [13-14].

Case Report

We report a clinical observation of patient, 36 years old, female sex, she’s still menstruated. A right mammary nodule has been discovered in October 2009, and has been constantly increasing in size without any associated inflammatory signs, or clinical lymph nodes invasion.

A bilateral mammography was done and chirurgical exerese has been preformed two month later revealing an invasive lobular carcinoma (ILC), measuring 6.5 cm, Scarff Bloom Richardson (SBR) grading was II with nuclear mitosis grade 2.

The tumorectomy was subsequently completed by a mastectomy associated to an axillary lymph node dissection. The pathology does not find any residual tumour but revealed infiltrating lymph node in 15 lymph nodes of the 16 preleved with an ILC, SBR II The search for hormonal receptors (HR) revealed a positive status (RE 30%; RP 70%), HER2 was found also positive (HER2 3+) in IHC study (Hercept Test - Dako) with an intensive and total marquage in 50% of the tumoral cells.

A workup for searching metastatic localisation has been performed, comprising Thoraco-Abdominal CT-Scan and bone scintigraphy, displayed metastatic localisations in bone and one hepatic localisation measuring 20mm. The tumoral marker CA15-3 was elevated (38 UI/ml).

It was decided to use a sequential combination chemotherapy with 3 cycles of AC-60 (Doxorubicine 60mg/m2-Day1, Cyclophosphamide 600mg/m2-Day1) and 3 cycles of Docetaxel 100mg/m2 associated with Trastuzumab. The evaluation after 6 cycles objective a complete response in the hepatic localisation and
Discussion

To confirm the originality of our case, we carried out a literature review by using the Pubmed database, with the following key words: breast cancer, ILC, HER2. We present here the results concerning breast cancers ILC subtypes associated with HER2 positive phenotype. Those findings will be discussed thereafter.

Results of ILC – HER2 positive

Lobular carcinomas were less likely than ductal carcinomas to have HER2neu amplification or overexpression, the positive phenotype of this gene has been found in less than 1% of classical ILC. Hoff has found only 1 case with HER2neu amplification of 67 ILC studied (1.5%), but this case was re-examined revealing a pleomorphic variant of lobular carcinoma, with a nuclear grade 3. Another case was taken initially as ILC with HER2neu amplification, determined to represent not an ILC but rather an invasive ductal carcinoma (SBR grade 2) after re-examination by 3 pathologists [15]. Bilous reported also only 1 case with HER2 overexpression (scored as 3+HER2 positive) of 124 ILC (0.8%) and similary to Hoff, this was a grade 3 pleomorphic type[16].

In others studies published but with small effective of classical ILC (range, 13-50), HER2 overexpression was absent in all cases [17-19]. In contrast with these studies objectiving the rarity of this association (ILC with positive HER2), others authors reported a variable incidence (range 6%, 43%) [20-25].

In a large cohort of 263 ILC tested, Arpino found 28 ILC with HER2 overexpression (10.7%), the author conclude that may not be the classic ILC subtype but possibly a variant pleomorphic or mixed ILC–IDC categories [23].

ILC subtypes have been reported to have different biologic characteristics and clinical behaviour as compared with the classical ILC, especially for HER2 according to the high rate of HER2 positivity among cases of pleomorphic variant of ILC reported on few studies; Middleton found HER2 overexpression (IHC, HER2 2+/3+) in 81% of pleomorphic ILC [26]. Frolik reported a rate of 53% in SBR grade 3 pleomorphic ILC [27].

ILC and IDC have distinctive biologic characteristic, especially for HER2 expression. However, Rosen in a study of HER2 expression and tumour phenotype, reported HER2neu amplification in ductal and lobular carcinomas, and they found almost equal rates of amplification in these groups: 49% and 43% respectively. But the low cut off used of immunohistochemical test and the possible inclusion of pleomorphic variant may have been due to overinterpretation of the results with false positives cases included [25].

The discrepancy in the reported rates of HER2 positivity in ILC may be accounted by variation in histological type of ILC or antibody sensitivity and specificity in IHC.

The presence of HER2neu amplification or overexpression in pleomorphic lobular carcinoma (PLC) is not surprising, given its high nuclear grade, and to the fact that the genomic profile of PLC is similar to high-grade IDC according to the recent studies published [28,29]; therefore an HER2 positive in classical ILC should prompt reevaluation of the tumour to exclude the possibility of misclassification.

Molecular characterization of ILC has shown that they have a higher incidence of loss of chromosome 17q than ductal carcinomas, also a low incidence of 17q22–24 amplification, gene location of HER2neu, than their ductal counterparts.[29,30]

Testing for HER2 positivity is primordial in the management of patients with breast cancer, either at the time of diagnosis or at the time of disease recurrence. Trastuzumab has shown to have clinical benefit in adjuvant and metastatic disease, the international guidelines recommend the introduction of Trastuzumab with chemotherapy independently on the histological subtype of breast cancer. Management decisions should be based on individual patient and tumour biologic characteristics, and not on lobular histology.

Despite the fact that the biologic phenotype of ILC is quite favourable, Rosenthal found an adverse outcome if HER2neu gene amplification is associated, the amplification can predict disease-related death in lobular cases independently (p=0.003) [21]. Because of the low probability of HER2 positivity in classical ILC, some authors suggest that it may not be necessary to test for HER2 in this subgroup breast cancer[16]. But due to the current benefice in overall survival of Trastuzumab in the adjuvant setting, and to the fact that diagnostic of classical ILC may be confused with the pleomorphic variant, we think and recommend that all the breast cancer should be test for HER2.
Conclusion

We report an atypical case of classical ILC overexpressing HER2 that reexamined by two different pathologists.

The literature review showed a rarity of typical ILC associated to HER2 positive phenotype, but the studies include small cohorts and report variable incidences due to the possible inclusion of ILC variant such a pleomorphic type. Large data including only a confirmed classical ILC are needed to confirm the rarity of this finding.

We suggest reexamination of tumours diagnosed as lobular carcinomas if the lesion displays HER2 positivity to assure the exclusion of missed ductal components.

References

Illustrations

Illustration 1

Table 1: ILC and HER2 positive (overexpression or amplification)

<table>
<thead>
<tr>
<th>Author – Date</th>
<th>ILC (n)</th>
<th>Assay</th>
<th>HER2 + (N)</th>
<th>HER2 + (%)</th>
<th>Subtype of ILC-HER2+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classical ILC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porter Pl -1991</td>
<td>15</td>
<td>IHC</td>
<td>0</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Frolik.D -2001</td>
<td>15</td>
<td>IHC</td>
<td>1</td>
<td>6.5%</td>
<td>Classical ILC, SBR grade1</td>
</tr>
<tr>
<td>Hoff ER -2002</td>
<td>67</td>
<td>FISH</td>
<td>1</td>
<td>1.5%</td>
<td>Pleomorphic, SBR grade2</td>
</tr>
<tr>
<td>Bilous M -2003</td>
<td>124</td>
<td>IHC</td>
<td>1</td>
<td>0.8%</td>
<td>Pleomorphic, SBR grade3</td>
</tr>
<tr>
<td>Bane AL -2005</td>
<td>50</td>
<td>IHC</td>
<td>0</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Reis-Filho JS -2006</td>
<td>15</td>
<td>IHC</td>
<td>0</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td><strong>No precision of ILC subtype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosen.PP -1995</td>
<td>np</td>
<td>FISH</td>
<td>Np</td>
<td>43%</td>
<td>No precision</td>
</tr>
<tr>
<td>Rosenthal SI -2002</td>
<td>71</td>
<td>FISH</td>
<td>9</td>
<td>13%</td>
<td>No precision</td>
</tr>
<tr>
<td>Arpino.G -2004</td>
<td>263</td>
<td>IHC</td>
<td>28</td>
<td>10.7%</td>
<td>No precision</td>
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<tr>
<td>Aiaga.R -2005</td>
<td>128</td>
<td>FISH</td>
<td>8</td>
<td>6%</td>
<td>No precision</td>
</tr>
<tr>
<td>Turashvili G -2007</td>
<td>14</td>
<td>FISH</td>
<td>Np</td>
<td>8%</td>
<td>No precision</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>FISH</td>
<td>3</td>
<td>25%</td>
<td>All cases: ILC SBR grade3</td>
</tr>
</tbody>
</table>
Pleomorphic ILC

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases (IHC)</th>
<th>IHC</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middleton LP 2000</td>
<td>21</td>
<td>17</td>
<td>81%</td>
</tr>
<tr>
<td>Frolik D 2001</td>
<td>15</td>
<td>8</td>
<td>53%</td>
</tr>
</tbody>
</table>

All cases: SBR grade 3

FISH (Fluorescence In Situ Hybridization), IHC (Immunohistochemical test), SBR (Scarff Bloom Richardson grading) ILC (Invasive Lobular Carcinoma).
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