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Review article

Basal-like subtype of breast carcinoma: An enigmatic group of tumors

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RESUMEN

El perfil de expresión de genes ha desafiado el sistema tradicional de clasificación histopatológica y ha clasificado a los carcinomas infiltrantes de la mama en cinco subgrupos distintos: carcinoma semejante a la glándula mamaria normal, luminal A, luminal B, con sobreexpresión de HER2 y carcinoma de fenotipo basal. Inicialmente, el subgrupo de carcinoma de mama de fenotipo basal se caracterizó por un patrón morfológico y un perfil inmunohistoquímico específicos (expresión de citoqueratinas de fenotipo basal, negatividad para receptores de estrógeno y de progesterona y HER-2), pero también por un resultado clínico malo. Sin embargo, más artículos recientes han mostrado que el carcinoma de mama de fenotipo basal no es un subgrupo uniforme de tumores, sino un grupo heterogéneo, que incluye tumores que pueden mostrar morfología, grado histológico, características inmunohistoquímicas y respuesta a la quimioterapia diferentes. Además, existen resultados contradictorios en la bibliografía con respecto al resultado global de los pacientes con este tipo de carcinoma de mama, probablemente debido a la falta de criterios estrictos para definir la lesión, que también pueden afectar el número de tumores publicados y reconocidos como de esta categoría. Ahora se necesitan criterios precisos para estandarizar los estudios clínicos en este grupo de tumores, que podrían curarse con diferentes estrategias terapéuticas.
Palabras clave: mama, genotipo basal, perfil de la expresión de genes.

ABSTRACT

Gene expression profiling has challenged the traditional histopathological classification system and classified infiltrating breast carcinomas into five distincte subgroups: normal breast-like, luminal A, luminal B, HER 2 overexpressing and basal-like carcinoma. Initially, basal-like breast carcinoma subgroup was characterized by a specific morphological pattern and immunohistochemical profile (expression of basal-like cytokeratines, negativity for estrogen, progesterone receptors and HER-2) but also by a poor clinical outcome. Hovewer, more recent papers have shown that basal-like breast carcinoma is not a uniform subgroup of tumors but a heterogeneous one, comprising tumors that can present different morphology, histological grade, immunohistochemical features and response to chemotherapy. Even more, there are contradictory results in the literature concerning the overall outcome of the patients with this type of breast carcinoma, probably due to a lack of strict criteria to define the lesion, that can also affect the number of published and recognized tumors within this category. Precise criteria are now needed to standardize the clinical studies on this group of tumors that could benefit from different therapeutic strategies.
Key words: mama, genotipo basal, perfil de la expresión de genes.

Breast cancer is one of the most frequently malignant tumor diagnosed in women worldwide.[1] The most important traditional parameters currently used in order to asses the prognosis and determine the appropriate therapy in patients with breast cancer are the following: age of the patient, presence of the axillary lymph node metastases, tumor diameter, histological type, histological grade, Ki-67 index, estrogen and progesterone receptors (ER and PR) and HER 2 status.[2,3] But even combining these factors there is a limitation in the evaluation of the prognosis in individual patients since in breast cancer, patients with similar parameters may have different clinical courses.[4] Taking into consideration these parameters, there is also an inabillity to predict therapeutic response in each patient. Therefore, better methods are needed to assess the prognosis and determine which treatment is more indicated in every patient with breast cancer.

During the last decade, in order to achieve this goal, molecular techniques have been used, specially the gene expression profiling that has a greater potential to refine

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breast cancer classification and to improve the patient's management. Using this method, distinct subtypes of breast cancer associated with different survival have been defined.[5,6] Among these, basal-like breast carcinoma was initially shown to be associated with the worse survival.[6] This paper reviews the most important papers published on basal-like carcinoma of the breast in order to determine whether this is a distinct entity with a different outcome that may need different therapeutic schemes. Contradictory results from recently published papers emphasize that basal-like carcinoma of the breast is a subgroup of tumors comprising a spectrum of different morphological and immunohistochemical entities that have different prognosis.

DEFINITION OF BASAL-LIKE BREAST CARCINOMA

Using the gene expression profiling (a method based on cDNA microarray in order to explore gene expression patterns), Perou et. al and Sorlie et. al. have published two papers in which breast tumors have been classified into five subgroups with significantly different gene expression profiles, clinical and morphological features, response to treatment and potential prognostic significance.[5,6] The five different subgroups are the following: normal breast-like, luminal epithelial A, luminal epithelial B, HER 2 overexpressing and basal-type carcinoma.[5,6] Each subtype of tumor expresses a distinct set of genes. Basal-like breast carcinomas were so named because the neoplastic cells composing this tumor type express genes usually found in normal basal/myoepithelial cells of the breast and they account for up to 15% of all breast cancers.[7] These two studies challenged the traditional histopathological classification system, according to which breast carcinoma has been classified into: infiltrating ductal carcinoma, infiltrating lobular carcinoma, tubular carcinoma, mucinous carcinoma, medullary carcinoma, papillary carcinoma, metaplastic carcinoma, apocrine carcinoma and very rarely and uncommonly other types (Tavassoli, 2003). The results of the studies performed by Perou et. al. and Sorlie et. al. concluded that the HER2 overexpressing tumors and the basal-type tumors were two subgroups associated with the shortest disease free survival and overall survival, emphasizing that the basal-like tumors may represent a distinct clinical entity.[5,6] They have also concluded that luminal A subtype is a distinct group that has a better prognosis than luminal B. The results of these two papers have been commented by Moinfar in a paper published in 2008,[8] in which he stressed some of the weak points of the two publications:

a. The importance of an appropiate reference sample as an internal standard, composed exclusively of normal breast for genetic comparison (in the two studies the authors have used a mixture of highly heterogeneous cell lines of epithelial, mesenchymal and hematologic cancers of different organs as a control).
b. The small number of total cases (39 in the Perou study and 78 cases in the Sorlie study) and small numer of basal-like carcinoma cases (6 cases in the Perou study and 7 cases in the study performed by Sorlie) to reach a conclusion as well as for statistical analysis.[5,6]
c. The lack of luminal-type cytokeratins as CK 8/18 and/or CK 19 that are not shown in the luminal subtype ER-positive described by Perou et. al.[5]
d. The lack of a cutoff for positive immunoreaction in tumor cells of the basal-like subtype regarding the immunohistochemical studies performed in both papers (the basal-like carcinoma being characterized by basal-type cytokeratines as CK 5 and/or CK 17 in all the reported cases).[5,6]

However, heterogeneity has been identified even within basal-like carcinomas subgroup in subsequent publications, regarding immunohistochemical profile, morphology and clinical outcome and no widely-accepted definition of this category of breast tumors is available so far.[9-11]

CLINICAL FEATURES OF BASAL-LIKE CARCINOMA OF THE BREAST

The tumors included in the basal-like category and called *basal-like breast carcinomas* are characterized by specific gene expression profiling but also by immunohistochemical features (immunoreactivity for basal-type cytokeratins, epidermal growth factor receptor and negative for ER, PR and HER 2). This category of tumors is more frequently encountered in African American women and in patients that are more likely to be BRCA 1-associated (although the reason is unclear). There is no significant association between basal-like breast carcinoma and BRCA 2 gene mutation at present. Patients with basal-like breast carcinoma have a shorter survival compared with those that have developed other molecular subtypes.[12,13] They

are usually highly proliferative tumors and for this reason they can achieve rapid clinical growth rates, being over-represented among cancers arising between annual mammograms.[14,15] The average age varies from 47.7 to 55 years.[12,16,17] Some of the studies demonstrated that basal-like breast carcinoma occur more frequently in younger patients while others did not find differences between this group and the nonbasal-like carcinomas.[17,18]

IMMUNOHISTOCHEMICAL PROFILE

Since gene expression profiling is a method that cannot be applied in every laboratory, basal-like carcinoma of the breast is generally defined in the most recently published papers using the immunohistochemistry profile combined with the histological features. In a normal breast tissue, epithelial cells usually express CK 7, CK 8, CK 18, CK 19, ER and PR while the myoepithelial cells express CK 5/6, CK 14, CK 17 and myoepithelial markers such as p63, CD 10, calponin, actin, but never express ER and PR.[3] There is no international consensus on the accepted markers that could define basal-like breast carcinoma or the percentage of positive tumor cells for every marker as a cutoff. Initially, in the papers published by Perou[5] and Sorlie,[6] basal-like breast carcinoma was defined using CK 5/6 and CK 17. However, since then a number of papers that have examined basal-like tumors used different other basal-like cytokeratins, single or in a combination of two, such as CK 5, CK 14, the positivity for these markers being reported as heterogeneous and focal.[16,19] The most frequently expressed marker was found to be CK 5/6 in up to 70% basal-like carcinomas, followed by CK 14 in 41.2% carcinomas and least frequent was CK 17.[16,20] Other publications mentioned that the tumors included in this category are negative for ER, PR and HER2 (so-called triple negative tumors) in addition to expression of basal cytokeratin and epidermal growth factor receptor (EGFR).[16,21] It was also observed that the vast majority of basal-like carcinomas can express both luminal-type cytokeratin (CK 8, 18, 19) and vimentin.[20-22] The expression of luminal-type cytokeratins is much more intense and diffuse in basal-type carcinoma than the basal-type cytokeratins. A positive reaction for c-kit (CD117) can be also identified in basal-like carcinoma of the breast.[20-22] Myoepithelial markers such as actin, CD 10, p63 can be also positive, indicating that some of these tumors can have a myoepithelial differentiation and possible a myoepithelial origin.[23] Half of the cases have p53 gene mutation with immunoreactivity to p53 protein.[13,16] High Ki-67 index was observed in 67% of cases and positivity for P-cadherin in 83% of cases.[24,25] Haupt et al. have recently proposed a panel of markers that includes: ER (-), PR (-), HER2 (-), 1 basal CK (+), HER1(+) and/or c-kit (+) to define basal-like carcinoma of the breast, also having been proposed by other authors.[21,26,27] This panel has a specificity of 100% and a sensitivity of 76% for the identification of basal-like cancers.[21]

The lack of strict criteria to define basal-like carcinoma affect the number of diagnosed and published cases in the literature. Even more, in most of the publications on basal-like breast carcinoma there is no explanation on how the type of the marker used to define such a lesion or the percentage of positive tumor cells for any of the markers could influence the results concerning the overall survival or disease free survival of these patients.

PATHOLOGIC FEATURES OF BASAL-LIKE BREAST CARCINOMA

In the initial study of Perou[5] they have examined 39 cases of malignant breast tumors, 36 of which were infiltrating ductal carcinomas, 2 were infiltrating lobular carcinomas and 1 was an *in situ* carcinoma. In the second paper, Sorlie[6] examined 78 breast carcimomas comprising 71 infiltrating ductal carcinomas, 5 infiltrating lobular carcinomas and 2 *in situ* ductal carcinomas. Both studies have focused mostly on the infiltrating ductal carcinoma probably the main reason why all the basal-like carcinomas were of grade 3 infiltrating ductal carcinoma. The basal-like carcinoma as described by other subsequent publications was usually but not always a poorly differentiated infiltrating ductal carcinoma NOS-type (not otherwise specified), with pushing margins, abundant peritumoral inflamatory infiltrate, geographic necrosis, central fibrotic focus, solid architecture, high nuclear grade, high mitotic index and no association with ductal carcinoma *in situ* (DCIS).[20]

However, using immunohistochemical markers it appeared that basal-like carcinomas have a more heterogeneous phenotype and some other morphological aspects can be encountered: metaplastic carcinoma (including low-grade adenosquamous carcinoma, spindle cell carcinoma, squamous cell carcinoma, mucoepidermoid

carcinoma, carcinoma with heterologous chondroid and/or osseous differentiation, carcinosarcoma), adenoid-cystic carcinoma, medullary carcinoma and so-called atypical medullary carcinoma.[20,28-30] (Figures 1 and 2) Rare cases of carcinomas arising from microglandular adenosis may also display a basal-like phenotype as well as a variety of other histological subtypes.[31] It is also important to mention that even most examples of basal-type carcinomas are high grade tumors there are also low-grade breast carcinomas with a characteristic basal-like immunohistochemical profile (as low grade adenosquamous carcinoma, secretory carcinoma). These tumors do not have a solid pattern, atypical nuclei or high mitotic index.

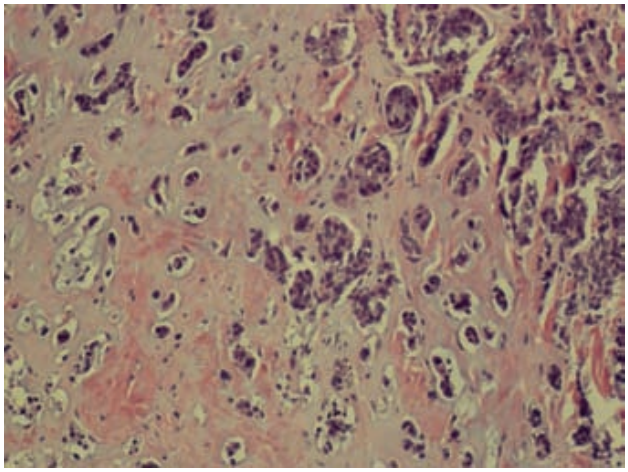

Figure 1. Microscopic features of a metaplastic breast carcinoma. Color figures of this article appear in the appendix 3 of this issue.

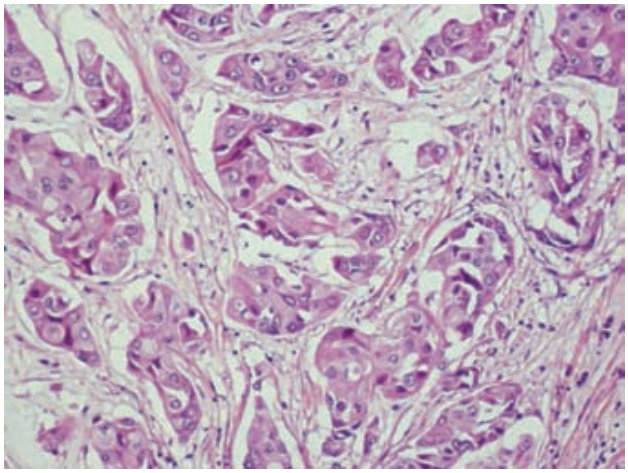

Figure 2. An example of high grade invase ductal carcinoma not otherwise specified.

There is no solid argument that basal-like carcinoma has a precursor lesion although in a small number of *in situ* ductal carcinoma cases there is a similar immunohistochemical profile with the infiltrating basal-like carcinoma (also described in the original paper of Perou) and in some cases of infiltrating basal-like carcinomas, an *in situ* component can be observed at the periphery of the tumor.[5,21,27]

Regarding the size of the tumor, most of the publications did not find any correlation between tumor size and gene expression profile.[32]

CLINICOPATHOLOGICAL FEATURES AND ASSOCIATION WITH PROGNOSIS

Sorlie et al. studied 49 patients with locally advanced breast cancer not associated with distant metastases (mean follow-up of 66 months) and of these, the group comprising 7 basal-like carcinomas had the worse prognosis.[6] Since the paper published by Sorlie, conflicting results have been observed by other investigators in the same field. To summarize them, some papers done on a large number of cases admitted that basal-like breast carcinoma is a distinct entity with genetic and clinicopathological characteristic features that is associated with a poor overall survival and/or disease-free survival and that the expression of basal cytokeratins is an independent prognostic factor in basal-like tumors not associated with lymph node metastases.[13,33-35] In other papers, however, the authors did not find a poor outcome associated with this subtype,[10,16,19,21,36] whether others found differences in the prognosis of basal-like carcinomas only in patients without lymph node metastases[35] or only in patients in whom lymph node metastases were present.[37] For example, in the Nielsen paper, the HER2+ group of tumors had a shorter survival than the basal-like group.[21] One study found that the prognosis of basal-like tumors with negative lymph nodes was the same as that of nonbasal-types in the first five years of follow-up but for more than five years follow-up the prognosis of basal-like tumors was better.[10] Moreover, most of the publications that mentioned the poor prognosis of basal-like breast carcinoma does not have a good selection of the cases since they did not include special subtypes of basal-like tumors that are low grade and low mitotic index, which can also be triple negative (for ER, PR and HER2) and positive for basal-type cytokeratins. Thus, most of the studies did not

compare the outcome of the basal-type breast carcinomas with nonbasal-type ones. On the other hand, most of the publications did not have strict immunohistochemical criteria to define basal-like breast carcinoma that were included in the study or did not use more than two myoepithelial markers in order to define the lesions.[13,33] Also, in the multivariate analysis some of the important prognostic parameters were not included.[33]

Regarding the metastasis, a recent publication has found that basal-like breast carcinoma is more frequently associated with brain metastasis and less associated with liver and bone metastasis than nonbasal type.[10] Basal-like breast carcinomas are also associated with the highest rate of complete pathological response to neoadjuvant chemotherapy according to one study,[38] but other studies did not find any association.[39]

CONCLUSIONS

In summary, basal-like breast carcinoma was initialy recognized as a distinct category of tumors based on gene expression profiling. Some of the published studies have shown evidences that support a worse prognosis and shorter survival associated with this subgroup of tumors, altough some more recent papers published conflicting results. The differences are due to the lack of internationally agreed definitions including uniform immunohistochemical definitions. Most of the papers did not show that basal-type cytokeratins expression has a prognostic value in grade 1 and 2 tumors and it is not clear whether grade 3 nonbasal-like carcinomas behave differently from grade 3 basal-like ones. Moreover, basal-like breast carcinomas and triple negative ones are not synonyms. Analysis of ER, PR and HER2 status of breast cancers classified by microarray-based expression profiling analysis as pertaining to the basal-like subgroup has revealed that 15-50% of them express at least one of these markers.[21] The basal-like breast carcinomas obviously do not represent a single uniform group of tumors but a spectrum of tumors from low-grade to high-grade with different morphology, chemotherapy response and different overall outcome.

Better characterization of the gene expression profile of these tumors and finding optimal treatment modalities are needed in the future. Since this subgroup of tumors is usually negative for ER and PR, they do not benefit from endocrine therapies or trastuzumab, but are likely to benefit from systemic chemotherapy. Basal-like breast cancer may represent a group of breast cancers that could benefit from EGFR-targeted therapeutical strategies, since EGFR is immunohistochemically overexpressed in more than 50% of cases.

The coexpression of basal and luminal cytokeratins together with the positivity of the basal-like tumors of the breast for vimentin suggest the possibility that these tumors may arise from stem cells that subsequently undergo variable degrees of basal and luminal differentiation. However, more studies on the origin of these tumors are neded in the future.

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