Triple negative breast carcinoma: the good, the bad and the ugly

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Abstract

Triple-negative breast cancers (TNBC) are a heterogeneous group of breast cancers defined by their lack of expression of oestrogen and progesterone receptors as well as human epidermal growth factor receptor 2 amplification, and therefore, are resistant to hormonal and Trastuzumab therapy. TNBC accounts for 15% of all breast cancers, and are more common in African-American women than in Whites. Also, BRCA-1 associated tumours are usually TNBC. Since the majority of TNBC fall into the basal-like breast cancer category by molecular studies, they are generally regarded as tumours of poor prognosis. However, some TNBC, such as adenoid cystic carcinoma and medullary carcinomas have excellent prognosis. Others, like metaplastic carcinoma have a prognosis that is comparable to infiltrating ductal carcinoma, not otherwise specified (NOS). Many immunohistochemical markers have been studied as an adjunct tool in classifying TNBC. However, microscopic evaluation remains an important tool in classifying these tumours and therefore predicting their prognosis.

Keywords adenoid cystic carcinoma; basal-type carcinoma; CK5/6; EGFR; hereditary; IMP-3; Ki-67; medullary carcinoma; metaplastic carcinoma; triple negative breast cancer

Background

Triple-negative breast cancers (TNBC) are a heterogeneous group of breast cancers that are traditionally defined by their lack of expression of oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (Her2/neu) expression. TNBC accounts for about 10–15% of all breast cancers. Population-based studies show that women with high body mass index and those who reported no recreational physical activity are at a higher risk for developing TNBC than women who are physically active and those with low body mass index.[1,2] Interestingly, some factors that are known to decrease the risk of breast cancer in general, do increase the risk for TNBC. These include first childbirth at an early age and multiparity. Racial disparity is also well-documented, with African-American women having the highest incidence rates for TNBC, followed by Hispanic women.[3] The negativity of these tumours for ER and PR as well as their lack of Her2/neu over expression, render them resistant to hormonal and trastuzumab (Herceptin) therapy, and makes treatment a challenging task. DNA microarray studies have classified breast cancers into four major types based on their molecular profile.[4] These include luminal type A and B, Her2/neu type and basal-like type. The prognosis varies among the four groups; with the basal-like type behaving the worst.[5] Although, collectively most TNBC fall into the basal-like category, there are different "faces" of TNBC with varying morphology and prognosis.

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The different faces of TNBC

Adenoid cystic carcinoma

First reported in 1952[6] adenoid cystic carcinoma (ACC) of the breast is a rare and morphologically distinct form of breast cancer, comprising less than 1% of all cases.[7] In contrast to other TNBC, the incidence of breast-ACC among Blacks is significantly lower than in Whites.[8] Histologically, these tumours are identical to their salivary gland counterparts. The tumour is composed of two cell types: cuboidal epithelial cells with rather abundant cytoplasm and pale nuclei lining tubular duct-like structures that contain neutral polysacchari des (PAS positive, diastase sensitive); and myoepithelial-like cells that elaborate acid mucopolysaccharides (alcian blue positive) and abundant basal lamina material. Mammary ACC can assume several architectural patterns including solid, cribriform (Figure 1a), tubular and trabecular configurations. These patterns may not be distributed homogenously in a given tumour causing potential diagnostic dilemma especially on core needle biopsies. A predominant cribriform pattern may be confused with invasive cribriform carcinoma, cribriform ductal carcinoma in-situ (DCIS) or even collagenous spherulosis. A panel of immunohistochemical stains including C-kit (CD117), P63 (Figure 2a & b), smooth muscle actin, heavy chain myosin and calponin is helpful in challenging cases.[9] ACC is usually positive for C-kit, P63 and smooth muscle actin but negative for both heavy chain myosin and calponin. Collagenous spherulosis and cribriform DCIS are positive for all myoepithelial cell markers but negative for C-kit. While invasive cribriform carcinoma do not express any of those markers. Although, typically negative for ER, PR and Her2-neu (Figure 1b–d), up to 12% of mammary ACC have been reported to be ER+/PR+.[8] DCIS in association with ACC is seen in a minority of cases, and may be difficult to distinguish form the surrounding nests of invasive carcinoma. The prognosis of ACC, as discussed later, is excellent.

Medullary carcinoma

Medullary carcinoma (MC) is a well-circumscribed tumour composed of high-grade cells arranged in sheets with intense lymphoplasmacytic infiltrate and no glandular formation. While there is no ultrasound or mammographic criteria for distinguishing medullary from non-medullary carcinoma, a tumour with irregular margin on imaging is unlikely to be a true MC. Although, MC is reported in the literature to range from 1 to 7% of all breast cancers, this wide range depends on the stringency of the diagnostic criteria used. In our practice, we occasionally see cases of atypical MC. However, we rarely encounter a pure

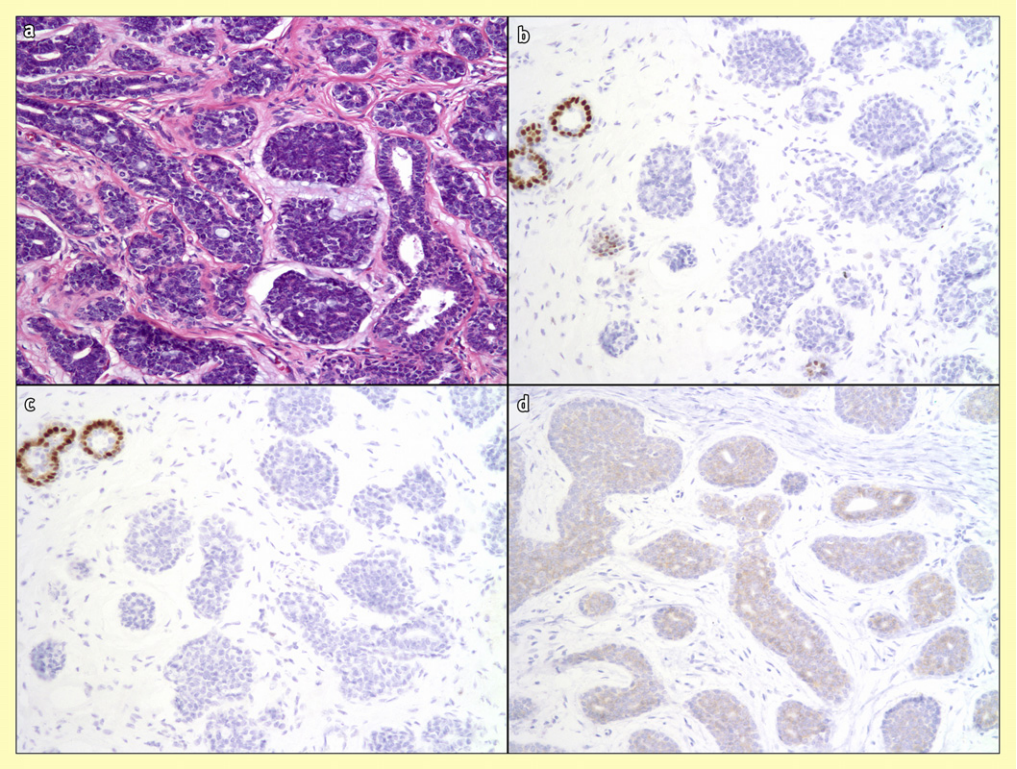

Figure 1 Adenoid cystic carcinoma: (**a**) H&E 200×; (**b**) Oestrogen receptor negative; (**c**) Progesterone receptor negative, Immunoperoxidase 200× (note positive internal control with residual breast ducts staining positive for ER and PR in top left corner); (**d**) HER-2 negative (not overexpressed), Immunoperoxidase stain 200×.

MC. A retrospective search in our surgical pathology files for the past decade, shows that we have not had a single case of pure MC in resection specimens, making this an extremely rare type of breast cancer, if strict criteria is applied. The Ridolfi system has the most stringent criteria,[10] while Pederson has the least stringent criteria.[11] Nevertheless, both classification systems recognize the following as mandatory microscopic features for the diagnosis of MC: syncytial growth pattern in more than 75% of

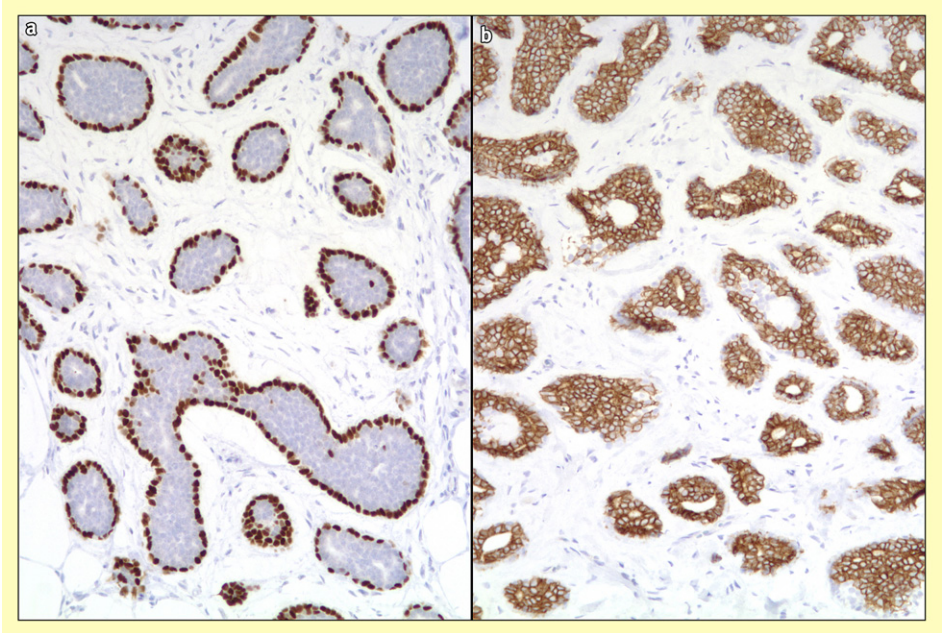

Figure 2 Adenoid cystic carcinoma positive for p63 (**a**) and CD117 (**b**), Immunoperoxidase stain 200×.