A Molecular and Morphological Deep-Dive Into Metaplastic Breast Cancers

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ABSTRACT: Metaplastic breast cancers (MBC) are relatively rare but account for significant global breast cancer mortality. Typically presenting without oestrogen and progesterone receptors or HER2 expression, these triple negative breast cancers are the archetypal 'stem cell-like' tumours that show a variety of metaplastic elements, including squamous, spindle, and chondroid. Given the vast heterogeneity in MBC by definition, large cohort studies are needed to draw conclusions. Together with our consortium colleagues, a cohort of 347 MBC was established, and a detailed morphological assessment made in an effort to understand the clinical relevance of the current diagnostic guidelines. Biomarker expression was investigated, and whole exome sequencing was performed. Herein, we provide an overview and contextualisation of the study.

KEYWORDS: breast cancer, molecular pathology, metaplastic, genomics, NF1

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In our recent paper, McCart Reed et al,[1] we described the application of a number of approaches to understand the pathology and biology of metaplastic breast cancers (MBC). Metaplastic breast cancers are a relatively rare (0.5%-5% of all breast cancers) breast cancer (BC) histological subtype that exhibits a stem-cell-like phenotype, with innate plasticity supporting differentiation into heterologous elements, including squamous, spindle, osseous, and chondroid. Metaplastic breast cancers typically lack expression of the oestrogen and progesterone receptors (ER/PR) and HER2, resulting in a 'triple-negative' phenotype with limited therapeutic options. These tumours are often large and account for significant global mortality from breast cancer.

We established the Asia-Pacific MBC consortium to bring together pathologists and researchers, and create a large cohort of tumour samples with detailed clinical data. The histological slides were reviewed by the pathologists over a multi-header microscope or via digital sharing of images, and classified using the World Health Organization (WHO)[2] definitions, which separates the tumours into 7 subtypes based on morphological features (WHO_1, mixed metaplastic carcinoma; WHO_2, low-grade adenosquamous carcinoma; WHO_3, fibromatosis-like MBC; WHO_4, squamous cell carcinoma; WHO_5, spindle cell carcinoma; WHO_6, MBC with mesenchymal differentiation: a, Chondroid; b, Osseous; c, Other [eg, rhabdoid]; WHO_7, myoepithelial carcinoma). These categories are understood to be descriptive yet pragmatic, with their clinical relevance largely unclear.

The morphology was correlated with clinicopathology information and breast cancer-specific survival where possible. Within the cohort of mixed metaplastic tumours (WHO_1; n = 251), the most frequent presentation, there were 32 combinations of morphologies, including 12 unique combinations. WHO_4 (pure squamous) MBC had the best survival outcomes over 10 years compared with either pure spindle (WHO_5) or the mixed category (WHO_1). The most significant indicators of poor prognosis were large tumour size (T3; $P = .004$), loss of cytokeratin expression (lack of staining with pan-cytokeratin AE1/3 antibody; $P = .007$), and Epidermal Growth Factor Receptor (EGFR/HER1) overexpression ($P = .01$), while EGFR negativity was associated with a favourable outcome. In the mixed MBC group (WHO_1), the presence of more than 3 distinct morphological entities conferred a significantly poorer outcome ($P = .007$) compared with those with fewer than 3; 16 cases of MBC with bizarre pleomorphic cells were noted. This pleomorphism was described as extreme, and there was a positive association between the presence of these highly atypical cells and the presence of spindle cell component.

We performed exome sequencing on 30 tumour/normal pairs. The variability in block age and origin in these tumour blocks was high and consequently there was a large range of sequencing quality, with an ultimate average of 29 somatic mutations per tumour. Breast cancer driver genes were the most frequently altered in this cohort: *TP53* (21/30 cases), *PIK3CA* (10/30 cases), *PTEN* (7/30 cases), and *NF1* (4/30 cases). We reported co-occurring mutations in *TP53* and *PTEN*, and in *PIK3CA* and *TP53*, and a highly significant enrichment for trios of co-occurring mutations in *TP53*, *PIK3CA*, and *PTEN* (n = 3/30; $P = .00003$) as compared with

TCGA (The Cancer Genome Atlas) breast cancer exome sequence data. Other studies have reported *PIK3CA* mutations from 23% to 61% of cases[3-5] confirming that MBC represent a genomically unique subgroup of triple negative BC, as the *PIK3CA* mutation frequency in other triple negative subtypes is only ~8%.[3] Exome and targeted sequencing studies have recently revealed frequent mutations in *TP53* (69%), *TERT* promoter (25%), *PIK3R1* (11%), *ARID1A* (11%), *FAT1* (11%), and *PTEN* (11%),[6,7] and also *NOTCH* and *MCL1*.[4,8] More data are emerging on the prevalence of specific mutations within the different morphological components of MBC. For example, Krings et al[4] showed that *TERT* promoter mutations were enriched (47%) in spindle cell carcinomas and tumours with squamous or spindle/squamous differentiation. Spindle cell carcinomas lacked *TP53* mutations, in contrast to other subtypes (78%, $P = .003$),[4] while chondroid tumours lack *PIK3CA* mutations.[4,6]

More research is needed to fully dissect the molecular profiles of the various metaplastic morphological subtypes and with this information would come a clearer understanding of whether the genetic alterations could be targeted therapeutically. It has been mooted that the high frequency of *PIK3CA* mutation makes MBC a candidate for *PIK3CA*-directed therapy; however, these drugs still require further optimisation for clinical implementation due to suboptimal tolerability.[9] Given that the *PIK3CA* mutations are not found in chondroid regions, such therapies may only target a proportion of the whole tumour, and strong genotype/phenotype diagnostic algorithms for the implementation of targeted therapies will need to be established to account for the vast heterogeneity in MBC. Indeed, combinations of targeted therapies may ultimately be required to produce meaningful responses in the entire tumour.

An unexpected finding of our study was the enrichment of *NF1* mutations (4/30 MBC compared with TCGA; $P = .0275$). Two of the *NF1* variations occur at nucleotide sites that are reported in COSMIC (Catalogue of Somatic Mutations In Cancer) as pathogenically mutated in melanoma (c.2850; Q950*), in squamous lung and colon cancer (c.1571; p.Glu524fs), and in breast cancer (c.1571; p.E524Q). *NF1* as a driver in breast cancer is established; however, there have been 6 recent case studies reporting 'rare' incidences of MBC presenting in patients with neurofibromatosis (NF1; inherited mutant *NF1* syndrome).[10-15] Recently, the **Mitogen-activated protein kinase (MAPK) 1** and 2 inhibitor, selumetinib, has shown benefit in the management of neurofibromas in neurofibromatosis patients,[16] and preclinical modelling shows promise in triple negative breast cancers.[17] With further development, this drug may become important in the management of a subset of MBC patients.

The extreme heterogeneity of MBC is a long way from being unravelled; however, the McCart Reed et al manuscript has provided interesting insights into the emerging molecular profile of MBC. Together with other recent studies, it is increasingly clear that pathology and genomics disciplines will need to work together to better understand these complex tumour types. Despite its limitations, the histopathology subtyping of MBC has been shown to provide valuable prognostic data, and exome sequencing has identified potentially targetable alterations. Strong morphologic associations of MBC subtypes with specific mutations require further large-scale investigation, and global moves towards diagnostic molecular pathology will underpin the clinical relevance of these findings.

Author Contributions

AMR and SRL drafted and reviewed the manuscript.

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