Carcinomas with medullary features

State of Play

Birgit Helmchen, Triemlispital Zürich

2012 WHO Definition of Carcinomas with Medullary Features:

Tumours demonstrating all or some of the following features:
- circumscribed or pushing border
- syncytial growth pattern
- cells with high grade nuclei
- prominent lymphoid infiltration

Included in this newly formed “special subtype” are:

- Medullary carcinoma ICD-O code 8510/3
- Atypical medullary carcinoma ICD-O 8513/3*
- Invasive carcinoma NST with medullary features ICD-O code 8500/3 **

* Code not given in the 2002 WHO Classification
**As any other invasive carcinoma NST
**Medullary breast cancer-The Long Goodbye**

*THE RELATIVELY FAVORABLE PROGNOSIS OF MEDULLARY CARCINOMA OF THE BREAST*

Oliver S. Moore, Jr., m.d.,* and Frank W. Foote, Jr., m.d.

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**Epidemiology**

**MBC Moore & Foote 1949**
- Medullary Carcinoma **5.2%**
- 52/1000 consecutive cases with radical mastectomy before Jan 1\(^{st}\) 1944

- Average age at Dx: **49 a**
- 9.6% diagnosed at <35 a
- 19% diagnoses at<40 a

**CMF WHO 2012**
- Classic MBC<1% *
- Higher rates have been reported depending on the stringency of the criteria used

- Average age at Dx: **45-52 a**
- 26% diagnosed at <35a

* No information on the prevalence of CMF as newly categorized.

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**Clinical Features**

**MBC Moore & Foote 1949**
- “Bulky”

**CMF WHO 2012**
- Often well-defined clinically and on imaging studies

(Not entirely untypical clinical information:
35y Female with 2cm lump right upper outer quadrant, clinically benign-Excisional biopsy-Fibroadenoma?)
**Macroscopy**

**MBC Moore & Foote 1949**
- Relative **softness** and gross anatomical **circumscription** are the rule
- Scattered **hemorrhages** not uncommon
- In other tumors yellowish **necrosis** predominates
- Extensive haemorrhage and necrosis (resulting in cyst formation)
- **Median diameter 3 cm** (range 1 cm-10 cm)

**CMF WHO 2012**
- Often **well-circumscribed soft** to moderately firm
- Frequent **haemorrhage**
- Frequent foci of **necrosis**
- Sometimes cystic degeneration
- **Median diameter 2-2.9 cm**

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**Histopathology**

**Moore & Foote 1949**
- The characteristic tumor of this type is made out of broad anastomosing cell masses
- The tumors appear more expansive than **infiltrative in their local growth tendencies** (description refers to macroscopy)
- Anastomosing sheets in sections (a certain papillary quality may be noted and alveolar tendencies may not be lacking)
- Lymphoid infiltrate is extremely common (believed to be intimate part of the lesion)
- The cellular make-up tends towards uniformity rather than great pleomorphism. The individual cells are large. Nuclei do not show great variation in hyperchromatism, size or shape, Mitosis are apt to be numerous
- “Medullary carcinoma of the breast, a readily recognizable tumor as here defined, possesses a significantly more favorable prognosis after radical mastectomy than do mammary carcinomas a a collective group”

**WHO 2012**
- Classically the following criteria were used to define MC
  1. Syncytial architecture in >75% of the tumour mass
  2. Histological **circumscription** or pushing margins
  3. Lack of tubular differentiation
  4. A prominent and diffuse lymphoplasmacytic stroma infiltrate
  5. Round tumor cells with abundant cytoplasm and pleomorphic high grade vesicular nuclei with one or several nucleoli. **Numerous Mitosis**. Atypical giant cells may be observed
- **These diagnostic criteria are DIFFICULT TO APPLY RESULTING IN……………**

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**Interoobserver Variability**
Refinement of Histopathological Criteria

MEDULLARY CARCINOMA OF THE BREAST
A Clinicopathologic Study with 10 Year Follow-Up

REN L. RIdolfi, MD, PAUL PETER ROSEN, MD, ABRAHAM PORT, MS, DAVID KINNE, MD, VALERIE MIKE, PhD

Ridolfi Criteria

<table>
<thead>
<tr>
<th>Typical Medullary Carcinoma</th>
<th>Atypical Medullary Carcinoma</th>
<th>Nonmedullary infiltrating duct carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synclital growth pattern (&gt;75%)*</td>
<td>Synclital growth pattern (&gt;75%)*</td>
<td>Syncial growth pattern &lt;75% and/ or presence of &gt;2 more other atypical features</td>
</tr>
<tr>
<td>And, one or two of the following:</td>
<td>And, one or two of the following:</td>
<td></td>
</tr>
<tr>
<td>Microscopically completely circumscribed</td>
<td>Focal or prominent tumor infiltration in areas of the margins</td>
<td></td>
</tr>
<tr>
<td>No intraductal component</td>
<td>Intracanal carcinoma present or dominant</td>
<td></td>
</tr>
<tr>
<td>Moderate to marked diffuse mononuclear stromal infiltrate</td>
<td>Mild or negligible mononuclear infiltrate, or infiltrate at margins only</td>
<td></td>
</tr>
<tr>
<td>Grade 2 or 3 nuclei</td>
<td>Grade 1 nuclei</td>
<td></td>
</tr>
<tr>
<td>Absence of microglandular features</td>
<td>Presence of microglandular features</td>
<td></td>
</tr>
</tbody>
</table>

*Note: Squamous, cartilaginous, or spindle cell metaplasia and areas of papillary differentiation did not influence carcinoma subclassification.

Life table analysis

Fig. 14. Revised life table analysis of survival after redistribution into typical medullary group of tumors originally classified atypical only because of intraductal carcinoma.

adapted from Eichhorn Seminars in Diagnostic Pathology, 2004
Confirmation of the Ridolfi Criteria

- 1988 Wargotz & Silverberg, Human Pathology
- 1988 Rapin et al, Cancer
- 1995 Reinfuss et al, JCO
- 2005 Vu-Nishio et al, Clinical Investigation
  - Significantly better 10-y survival rate for MC than for IDC-NOS
    - MC 94.9%, N=46 versus IDC-NOS 77.5%, N=1398, p=0.028
- 2012 Hueber et al, Annals of Oncology
  - Significantly better 14-y overall survival rate for MC than for IDC-NST in an unrestricted and a restricted cohort-analysis of 13 IBCSG-Trials
  - Full (unrestricted cohort): MC 76%, N=127 versus IDC-NST 64%, N=8096, p=0.0
  - Restricted cohort (only ER-negative cases): MC 89%, N=47 versus IDC-NOS 63%, N=1407, p=0.01

Histomorphological Diagnosis of Medullary Breast Cancer is problematic

- High inter-and intra-observer variability
- Sobering kappa values
- Poor diagnostic reproducibility with regard to prognosis


Current view of the WHO expert panel

The classical criteria are difficult to apply
- Resulting in poor inter-observer variability
- Therefore it is recommended that
  - classical MC,
  - atypical MC and
  - invasive carcinoma with medullary features be grouped within the category of

- Carcinomas with Medullary Features

Key Features of CMF

- Distinct histomorphology ✓
- Triple negativity
- Basel-likeness
- BRCA-ness
- Immunogenity
Immunoprofile

- Most often negative for ER and PR
- Most often negative for HER-2
  - “Triple negative”
- Variable expression of keratin 5/6 and 14, smooth muscle actin, EGFR, P-cadherin, p53 and caveolin
- Lymphoid infiltration shows a predominance of CD3+ T-Lymphocytes and increased levels of CD8 cytotoxic T-lymphocytes

Carcinomas with medullary features are most often “triple” negative

<table>
<thead>
<tr>
<th>IHC Marker</th>
<th>TMBC 1</th>
<th>IC with Medullary features 2</th>
<th>Invasive Carcinoma G3 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER-negative</td>
<td>89.5%</td>
<td>94.3%</td>
<td>18.9%</td>
</tr>
<tr>
<td>PR-negative</td>
<td>48.7%</td>
<td>77.1%</td>
<td>34.5%</td>
</tr>
<tr>
<td>Her-2 negative</td>
<td>97.7%</td>
<td>100%</td>
<td>76.2%</td>
</tr>
</tbody>
</table>

1 Jaquemir et al J Pathol 2005
2 Rodriguez Pinilla et al Am J surg Pathol 2007
3 Rakha et al Eu J Cancer 2009

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- Triple negativity ✓
- Basel-likeness
- BRCA-ness
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What to do sitting at the microscope?

- Medullary carcinoma ➔ Stick with Ridolfi Criteria
- Atypical medullary carcinoma ➔ Stick with Ridolfi Criteria
- Invasive carcinoma NST with medullary Features ➔ Make use of Immunohistochemistry
Basal-like Breast Cancer

What are we talking about?

- Currently no international agreement how to define a given breast cancer as “basal-like” based on morphology and immuno-histochemical profile
- WHO refers to the “Nielsen Basal Profile”
  - ER-negative
  - Her-2 negative
  - Keratin 5/6 positive
  - and/or EGFR-positive

Nielsen Criteria on our Index Case

- The EGFR- Stain was negative
Comparative immunohistochemical profiles (WHO 2012)

<table>
<thead>
<tr>
<th>IH-markers</th>
<th>tMBC</th>
<th>IC with MF</th>
<th>IC G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nielsen Basal Profile</td>
<td>Not evaluated</td>
<td>62.9%</td>
<td>18.9%</td>
</tr>
<tr>
<td>ER-neg</td>
<td>89.5%</td>
<td>84.3%</td>
<td>38.5%</td>
</tr>
<tr>
<td>PR-neg</td>
<td>48.7%</td>
<td>77.1%</td>
<td>34%</td>
</tr>
<tr>
<td>Her-2-neg</td>
<td>97.7%</td>
<td>100%</td>
<td>76.2%</td>
</tr>
<tr>
<td>Ck 5/6 pos</td>
<td>54.8%</td>
<td>60%</td>
<td>17.9%</td>
</tr>
<tr>
<td>P53-positive</td>
<td>69.3%</td>
<td>65.2%</td>
<td>26.2%</td>
</tr>
<tr>
<td>Ki67</td>
<td>54.5%</td>
<td>91.2%</td>
<td>63.2%</td>
</tr>
</tbody>
</table>

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The Copernican Turn- MOLECULAR CLASSIFICATION OF BREAST CANCER- dawn of high throughput technology and “omics”

- c Luminal, ER+ (A and B)
- d ERBB2
- e Basal *
- f Normal

* Many of the genes characteristic of breast basal epithelial cells were highly expressed in a group of six clustered tumours. All six of these tumours showed staining for either keratins 5/6 or 17 or both. Notably, these six tumours also failed to express ER and most of the other genes that were usually co-expressed with it.

Vanderbilt TNBC Subtypes


Taxonomic Problems with TNBC/Basal-like Breast Cancer

- Most TNBCs classify as the basal-like subtype based on the intrinsic subtype classification
- The terms TNBC and basal-like breast cancer are not synonymous
- 20% to 30% of clinical TNBCs are not basal-like by microarray analysis
- Significant numbers of basal-like breast cancers, express ER/PR and /or HER2

Badve S Basal-like and triple-negative breast cancers: a critical review with an emphasis on the implications for pathologists and oncologists. Mod Pathol 2011
Key Features of CMF

- Distinct histomorphology
- Triple negativity
- Basel-like
- BRCA-ness
- Immunogenity

Differential Diagnosis

- Moore & Foote 1949:
- WHO 2012:
  EBV associated lymphoepithelial like carcinoma in the breast
  in fact, when these tumors are situated well out toward the tail of the breast, it becomes very difficult to be certain on all occasions whether they constitute primary lesions or node metastases from some undetected primary. Only when a peripheral sinus is demonstrated can one be sure that he is dealing with a node metastasis. The whole pattern may be such that one would consider the possibility of the lesion being an ovarian dysgerminoma metastatic to node, a large reticulum-cell sarcoma, or even a nonpigmented melanoma.

DCIS, Lobulitis, Immunohistochemistry (and clinical context) is helpful to determine the presence of a primary breast cancer with MF. CAVEAT re Melanoma: MBC frequently express S100. Re intramammary LN Metastasis of IC-NST: LN-capsule/peripheral sinus helpful.

Genetics

- A large proportion of CMF are basal-like
- Genomic instability common
- Most tumors in Patients with germline mutations in BRCA1 have medullary features and are basal-like by IHC and/or gene expression
- Sporadic CMF show inactivation of BRCA via promoter hypermethylation and somatic mutation
- The most frequent somatic alteration detected is mutation of p53


Lobulitis is associated with younger age, TMBC and medullary phenotypes

From Gulbahce et al Human Pathologie 2014 H&E ×4 (A), ×10 (B), ×20 (C); CD3, ×20 (D)
**BRCA1**
- 1994 BRCA1 positionally cloned
- 1997 BRC1 mutated carcinoma frequently have medullary features
- 1994-2015 ongoing exploration of BRCA-function
  - BRCA1 protein is involved in multiple essential biological functions
  - As part of a multiprotein complex, BRCA1 repairs double-strand DNA breaks via the homologous recombination repair pathway

Miki et al., Science 1994
Breast cancer linkage consortium, Lancet 1997
Foulkes WD et al, J Pathol. 2013

**BRCA-ness**
- Working title for sporadic tumors that display inactivation of BRCA related genes and consequently have HR- Deficiency
- Currently no standard definition for BRCAness
  - Area of intense investigation
Therefore these Tumors should feature
  - Radiosensitivity
  - Differential sensitivity for Drugs that cause strand breaks eg. Platin-based Drugs
  - Sensitivity for Parp-Inhibitors based on the concept of synthetic lethality


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**Prognosis and Predictive Factors**

**WHO classification 2002**
- MC has been reported to have a better prognosis than the common IDC

**WHO classification 2012**
- MC was traditionally considered to be associated with a relatively favorable prognosis compared with grade matched invasive carcinoma NST
**WHO 2012**

- The **low level of reproducibility** of a diagnosis of MC
- Resulted in an increase in the use of the concept of “medullary-like features”
- In practice MC are treated like basal-like triple-negative carcinomas with **aggressive therapy**

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**Immunogenity**

"It may be reasoned that this rather characteristic lymphoid infiltrate indicates some maladjustment between tumor and host"

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**Background**

- Presence of prominent lympho-plasmacytic infiltrate is associated with good prognosis in Breast cancer
- Tumor infiltrating lymphocytes provide prognostic and possible predictive value in TNBC
- Levels of immune response genes are independent predictors of outcome in ER negative, highly proliferative BC

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**Subtyping of TNBC: Implications for Therapy**

<table>
<thead>
<tr>
<th>TNBC type Molecular Subtype</th>
<th>Gene Ontology</th>
<th>Therapeutic Targets/Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL1</td>
<td>DNA Damage Response and Cell Proliferation</td>
<td>cisplatin, PARP inhibitors</td>
</tr>
<tr>
<td>BL2</td>
<td>TP53, EGFR and MET Signaling</td>
<td>mTOR, Growth Factor inhibitors</td>
</tr>
<tr>
<td>IM</td>
<td>immune signaling</td>
<td>cisplatin, PARP inhibitors</td>
</tr>
<tr>
<td>M</td>
<td>EMT, Not, TGF, IGF1, Notch, Cell Proliferation</td>
<td>mTOR, Growth Factor inhibitors, Sox inhibitors</td>
</tr>
<tr>
<td>MSL</td>
<td>EMT, Not, TGF, MAPK, Rac, PI3K, PDGF</td>
<td>mTOR, PI3K, MEK and Growth Factor inhibitors</td>
</tr>
<tr>
<td>LAR</td>
<td>AR signaling, FASN and ESRD4 Signaling</td>
<td>AR antagonists, PI3K inhibitors</td>
</tr>
<tr>
<td>UNC</td>
<td>DNA Damage Response and Cell Proliferation</td>
<td>cisplatin, PARP inhibitors</td>
</tr>
</tbody>
</table>

* IM= immunomodulatory subtype overlaps with Carcinoma with medullary features

Abramson V.G. et al, Cancer 2014

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Moore & Foote, Cancer 1949

A new Era of Oncoimmunology? Possible Immunotherapeutic strategies for CMF/TNBC

- MAGE-A3 and MUC-1 tumor vaccines
- Immune checkpoint blockade*
- Blocking the immunosuppressors
- Adoptive T-cell therapy

Stagg J, Allard B, Therapeutic Advances in Medical Oncology 2013


Key Features of CMF

- Distinct histomorphology ✓
- Triple negativity ✓
- Basel-likeness ✓
- BRCA-ness ✓
- Immunogenity ✓

WHO 2012 concluding remarks

These results suggest that the relatively good outcome of carcinomas with medullary features may be related to the prominent lymphoplasmocytic infiltrate

The last word might not be spoken on ...

THE RELATIVELY FAVORABLE PROGNOSIS OF MEDULLARY CARCINOMA OF THE BREAST
Carcinomas with medullary features
Birgit Helmchen, Triemlispital Zürich

Literatur


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Schmidt M et al.: The humoral immune system has a key prognostic impact in node-negative breast cancer. Cancer Res. 2008
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