Management of patients presenting with axillary metastases and unknown primary

Andreas Makris
Mount Vernon Cancer Centre
Take home messages

- Breast MRI will identify many of the breast primaries that were not detected by mammography or US

- Treatment of the breast with mastectomy or radiotherapy is required to avoid a high risk of local relapse
Introduction

• Axillary metastases with unknown breast primary account for 1% of all breast cancers
• First described by Halstead in 1907
• Staged as T0 N1 (Stage II)
• Characteristics of T0 N1 patients similar to those with stage II disease
• A primary breast cancer in the axillary tail may be confused for an axillary node
• Limited literature with small retrospective studies
• No randomised control trials
• Comparisons from previous studies difficult as better imaging has reduced the number of occult breast primaries
Axillary nodes

• **Benign**
  – Infections (viral, bacterial inc. TB), trauma, inflammation (RA, SLE)

• **Malignant**
  – Lymphomas
  – Breast
  – Lung
  – GI
  – Pancreas
  – Stomach
  – Ovarian
  – Thyroid

• Breast is the commonest primary for women presenting with axillary nodes with adenocarcinoma or undifferentiated morphology
NICE Clinical Guidance (CG104)
Metastatic malignant disease of unknown primary origin in adults: diagnosis and management

• Organisation of services and support
  – Every hospital with a cancer centre or unit should establish a CUP team

• Diagnosis
  – Phase 1: aim is to perform the most appropriate investigations efficiently to identify
    • a primary site, which will guide treatment decisions
    • non-epithelial malignancy, which can be treated regardless of primary site (eg lymphoma, melanoma, sarcoma, germ-cell tumours)
    • metastatic epithelial or neuroendocrine malignancy without an identifiable primary site (a diagnosis of provisional CUP)
  – Phase 2: special investigations for patients with provisional CUP diagnosis
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• Immunohistochemistry
  – Use a panel of antibodies comprising CK7, CK20, TTF-1, PLAP, ER and PSA in all patients with adenocarcinoma of unknown origin

  – Use additional immunohistochemistry to refine the differential diagnosis, guided by the results of the panel of antibodies above and the clinical picture

• Gene-expression-based profiling
  – Do not use gene-expression-based profiling to identify primary tumours in patients with provisional CUP
Diagnostic work-up of unknown primary: IHC and Molecular Profiling

• Identify broad cancer type
  – Carcinoma
  – Melanoma
  – Lymphoma/leukaemia
  – Sarcoma
    - Cytokeratins
    - S100
    - CLA, CD20, CD3 etc
    - Vimentin, actin, c-kit etc

• If carcinoma or related, then identify its subtype
  – Adenocarcinoma
  – Squamous carcinoma
  – Neuroendocrine carcinoma
    - CK7, CK20
    - CK5, p63
    - Chromogranin, CD56, synaptomysin

• If adenocarcinoma, then predict possible primary site
  – Breast
  – Lung
  – Ovary
  – Colon
    - ER, PgR, HER2
    - TTF1
    - CA125
    - CDX2

Oien KA & Dennis JL. Ann Oncol 2012; 23: 271-77
Diagnostic work-up of unknown primary: Molecular Profiling

- A number of tests are commercially available
  - Oncofocus from Oncologica UK Ltd (costs £1,500)
  - Cancer type ID from bioTheranostics (costs $3,600)
  - Rosetta Cancer Origin Test, formerly miRview mets2 (costs $4,356)
  - Tissue of Origin from Cancer Genetics (costs $3,250)
  - Caris Molecular Intelligence from Caris Life Sciences (costs £3,480)
  - The FoundationOne test from Roche Foundation Medicine (costs £3,000)

- All use formalin-fixed, paraffin-embedded tissue and use small tumour samples

- Tumours difficult to distinguish in morphology and IHC also difficult for molecular profiling
- May contribute to the diagnosis of poorly differentiated tumours
Investigations of patient presenting with axillary nodes

- Confirmation of malignancy
  - Axillary node biopsy or excision

- Search for Breast Primary
  - Mammography
  - US
  - Breast MRI

- Search for primary and staging
  - CT scan
  - PET Scan
NICE Clinical Guidance (CG104)
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• Breast MRI
  – Refer patients with adenocarcinoma involving the axillary nodes to a breast cancer MDT for evaluation and treatment. If no breast primary tumour is identified after standard breast investigations, consider MRI to identify lesions suitable for targetted biopsy
Mammography
Case Study 1

• 33 year old presenting with enlarged right axillary nodes.
• US shows large abnormal nodes. Core biopsy shows metastatic adenocarcinoma probably of breast origin
• Mammograms normal
Case Study 1

Mammograms of patient with right axillary nodes

Courtesy of W Teh
Case Study 1

Courtesy of W Teh
Case Study 1

- MRI shows solitary indeterminate mass lesion in right retroareolar area occult on second look ultrasound
- Referred for MRI biopsy
- MRI biopsy – IDC grade 2 ER8 PR8 Her-2 negative
Case Study 1

- MRI can detect primary breast cancer disease site in up to 70%
- MRI has high sensitivity but low specificity
- MRI biopsy can confirm primary site of disease
- This can guide appropriate surgical management
Role of PET

PET has low sensitivity but high specificity

May be used to monitor response to treatment
Role of PET- Monitoring response
Treatment of patients presenting with axillary metastases and presumed breast primary
Treatment of malignant axillary nodes (presumed breast primary)

- Patients can present with operable nodes or fixed inoperable nodes

- Operable nodes can be treated with initial surgery of axillary node dissection or neoadjuvant therapy followed by axillary surgery. Neoadjuvant therapy can be chemotherapy +/- anti-HER2 treatment or endocrine therapy (in older patients with ER+ disease)

- Inoperable nodes are treated with primary chemotherapy +/- anti-HER2 treatment and surgery if sufficiently downstaged
Systemic treatment

• Systemic treatment is used based on ER, PR and HER2 according to clinical guidelines as would be used for patients with resected primary and node positive disease
  – Endocrine therapy
  – Chemotherapy
  – Anti-HER2 treatment (Trastuzumab, Pertuzumab)
Pertuzumab for patients with axillary nodes and occult primary

- NHS England
  - Pertuzumab for the neoadjuvant treatment of *locally advanced*, inflammatory or early breast cancer at high risk of recurrence (TA 424)

- CDF
  - Pertuzumab for 1st line treatment of *locally advanced* or metastatic breast cancer (PER1_ver3.2)
Axillary nodal metastases from carcinoma of unknown primary: a systematic review of published evidence

- Based on 26 retrospective studies, published between 1975 and 2006, with total of 689 patients
  - Incidence of 0.12-0.67%
  - Mean age 52.4yrs (66% postmenopausal)
  - After AND, 48% N1 and 52% N2/3
  - Among 446 patients who had mastectomy, an occult breast primary was identified histologically in 321 (72%)
  - MRI revealed primary in 96/162 patients (59%)

- Prognosis based
  - Nodal status
  - Treatment of axilla
  - Treatment of breast

Axillary nodal metastases from carcinoma of unknown primary: a systematic review of published evidence

• Outcome
  – 5-year survival ranged from 59-88% (median follow-up of 62 months)
  – Some studies compared survival with stage-matched patients with node-positive resected breast cancer and outcome reported as similar

Systemic treatment

In the systematic review by Pentheroudakis

- Chemotherapy used in only 40% of women
- Only 5 women (1%) received an anthracycline-taxane combination
- No information on use of neoadjuvant chemotherapy from individual studies
- As studies were small the impact on outcomes could not be determined
- Preceded the introduction of trastuzumab

Management of the axilla

- Axillary dissection provides prognostic information and local control

- Level I and II axillary node dissection has been used in the majority of published studies

- Axillary excisional biopsy and subsequent radiotherapy is an alternative

- Axillary relapse rates were higher when axillary dissection was not used and excision +/- radiotherapy used, but this is from an era when systemic treatment was less effective than what is currently used

Management of the breast

- Treatment options:
  - Mastectomy 59%
  - Whole breast radiotherapy 26%
  - Observation 15%

- When mastectomy was used breast malignancy was found in 72% of cases (with an additional 6% having DCIS)

- When the breast was not treated, a primary subsequently developed in the untreated breast in 42% of cases (46/110)

- Breast cancers developed in the untreated breast 4-64 months from diagnosis

Radiotherapy

• Whole breast radiotherapy as an alternative to mastectomy was first reported by Vilcoq et al in 1982
• Subsequent studies suggested similar local control and survival to mastectomies
• Doses of 40Gy 15# and 50Gy 25# can be used

• Chest wall radiotherapy after mastectomy is consistent with benefits from the EBCTCG overview in patients with breast primary and involved nodes

• Radiotherapy may also be needed to the upper axilla and/or SCF depending on the extent of nodal involvement. If axillary dissection has not been used the whole axilla should be treated

Conclusion

- Axillary metastases with unknown breast primary is an uncommon presentation of breast cancer
- Characteristics of T0 N1 patients similar to those with stage II disease
- Breast MRI will identify many of the breast primaries that were not detected by mammography or US
- Axillary dissection provides prognostic information and local control
- Chemotherapy may be used before or after surgery
- Chemotherapy before surgery is the treatment of choice in patients with large volume axillary disease
- For HER2 positive disease anti-HER2 therapy with trastuzumab and pertuzumab is used
- Treatment of the breast with mastectomy or radiotherapy is required to avoid a high risk of local relapse