Immunohistochemical differentiation of metastatic tumours

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Key points from a review article written by Daisuke Nonaka
Intro

- Metastatic disease is the initial presentation in 10–15% of cases (higher in carcinomas)
- In up to 1/3 of cases the primary tumour site may not be identified
- Common organs involved in metastasis
  - Lung, LN’s, liver, bone and brain
  - In these organs there is a higher incidence of mets than primary tumours
Intro

- In some cancers, there may be a long latent period before metastasis and therefore a detailed medical history together with radiological findings is essential.
- Such information allows you to narrow down the differential and therefore select relevant immuno
  - cost-effective and time-efficient
Undifferentiated tumours

- Can be classified into generic morphological categories:
  - Small round blue cell neoplasm
  - Spindle cell neoplasm
  - Epithelioid neoplasm
  - Pleomorphic neoplasm

- In each category, depending on age, sex, clinical history and location of metastasis, there would be a statistically probably differential diagnosis.
Immunohistochemistry

In metastatic undifferentiated tumours, immuno should aim at determination of the broad category of tumour groups –

- Carcinoma – Cytokeratin
- Melanoma – S100
- Lymphoma – CD45
- Sarcoma – Vimentin
- Germ cell tumour – no pan-germ cell tumour immuno
Carcinomas

- Cytokeratins are useful screening markers
- Poorly differentiated carcinomas show variable expression to CK’s
- EMA (epithelial membrane antigen) may serve as a supplement to CK’s especially in sarcomatoid or undifferentiated carcinoma that are –ve for CK.
- EMA however is negative in some epithelial tumours (endocrine, medullary thyroid) and are positive in some haematopoietic malignancies.
- Abberant CK staining in nonepithelial malignancy is weak and stains focally whereas CK staining in carcinomas is strong.
Germ cell tumours

- There is no pan-germ cell tumour immuno marker
- When germ cell tumours are suspected OCT3/4 detects components of seminoma and embryonal carcinoma
- OCT3/4 is a transcription factor and is fundamental in the maintenance of pluripotency in embryonic stem cells – its expression dissappears rapidly when cells differentiate.
- Combinations of CD30 and CD117 can help to distinguish between seminoma and embryonic carcinoma
  - Seminoma – CD30 – , CD117 +
  - Embryonal – CD30 +, CD117 –
Metastatic seminoma in a LN

OCT3/4 immuno
Malignant melanoma

- S100 in the screening marker for MM with >95% sensitivity.
- S100 however has a low specificity and is also expressed in other tumours –
  - Peripheral nerve sheath tumours
  - Occasional adenocarcinomas
- Therefore melanocyte–specific markers are used
  - HMB–45 (sensitivity 75–92%)
  - Melan A (sensitivity 69–93%)
- However, desmoplastic and spindle cell melanomas are negative for melanocyte–specific markers
Haematopoietic malignancies

- CD45 has high sensitivity (97%) and specificity (nearly 100%) for lymphoid tumours.
- However, CD45 is unexpressed in lymphoblastic lymphomas and variably expressed in plasma cell neoplasms and anaplastic large cell lymphomas.
<table>
<thead>
<tr>
<th>CK7 &amp; CK20</th>
<th>CK7</th>
<th>CK20</th>
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<tbody>
<tr>
<td>Colorectal carcinoma</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Ovarian, endometrial, lung, salivary gland or mammary gland carcinoma</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Urinary bladder</td>
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<tr>
<td>Squamous carcinoma</td>
<td>-</td>
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<tr>
<td>Urothelial carcinoma</td>
<td>+</td>
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<tr>
<td>Prostate carcinoma</td>
<td>-</td>
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</tr>
<tr>
<td>Urothelial carcinoma</td>
<td>+</td>
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<tr>
<td>Neuroendocrine</td>
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<tr>
<td>Merkel cell carcinoma</td>
<td>-</td>
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<tr>
<td>Small cell carcinoma of lung</td>
<td>+</td>
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Organ specific markers

- Lung – TTF-1
- Thyroid – thyroglobulin, calcitonin
- Adrenal – Melan-A, inhibin-A and calretinin are expressed in adrenocortical carcinomas
- Breast – ER & PR
- GI & pancreas – CDX-2
- Liver – HepPar-1
- Kidney – RCC, CD10
- Ovary – CA125
- Endometrium – ER, PR
- Prostate – PSA
Transcription factors

• Proteins that control the first step of gene expression.

• Orchestrates the complex pathways of cellular growth and differentiation.

• Some are tissue/organ specific therefore helpful for determining cell lineage of tumour
**TTF-1**

- Expressed in lung, thyroid and ventral forebrain
- Expressed in 75% of lung adenocarcinomas
- Usually negative in mucinous carcinomas and bronchogenic squamous cell carcinomas
- Consistently expressed in papillary, follicular Hürthle cell and poorly differentiated carcinomas of the thyroid
- Expressed in 18% of anaplastic and variably in medullary thyroid carcinomas.
Metastatic thyroid follicular carcinoma stained for TTF-1.
WT-1

- Normally expressed in developing human organs – kidneys, ovarian surface epithelium and mesothelium
- Usually negative in all endometrial carcinomas
- In ovarian carcinomas
  - positive in serous adenocarcinoma, transitional carcinoma, and small cell carcinoma
  - negative in clear cell, endometrioid and mucinous carcinomas
- Good marker for epithelioid malignant mesothelioma
- Useful to distinguish mesothelioma from adenocarcinoma of the lung
CDX-2

- Plays a critical role in the development of the intestines
- Useful marker for intestinal differentiation
- Expressed in 70–85% of colorectal adenocarcinomas which is also retained in metastatic foci
- Its expression declines in poorly differentiated carcinomas
- Also seen in adenocarcinomas of GOJ, stomach, ampulla and small intestine.
- Seen in 5–30% of pancreas ductal adenocarcinomas, cholangiocarcinomas and gall bladder adenocarcinomas.
CDX-2 staining in normal bowel

Ascending colon

B

Descending colon

C

Rectum

Adenocarcinoma of the colon
P–63

• Pivotal in the development and maintenance of stratified epithelia
• Expressed by
  • squamous epithelium, urothelium and thymic epithelium as well as
  • myoepithelial cells in breast, salivary, bronchial and sweat glands
  • basal cells of prostate
  • Bronchus
• Almost always expressed by SCC, thymomas, BCC, urothelial carcinomas and myoepithelial carcinomas
Fli-1

- Master regulator of the haemangioblast, a common precursor of blood and endothelium
- Expressed by endothelial cells of all types of vessel
- Positive in Ewing’s sarcoma/PNET, lymphoblastic lymphomas and malignant vascular tumours (angiosarcoma, epithelioid haemangioendotheliomas and Kaposi sarcomas)
- Also expressed in subset of Merkel cell carcinomas, malignant melanomas, synovial sarcomas, adenocarcinomas of the lung and breast.
Ewing’s sarcoma

Epithelioid angiosarcoma

Fli-1
Necrotic tumours

- Immuno may not work due to loss of antigenicity or may result in false positivity
- Immuno may be helpful in some situations
  - HMB-45 & Melan-A in malignant melanoma
  - CK, OCT3/4, CD30 & CD117 in germ cell tumours
- The necrotic cells that retain immunoreactivity correspond to areas where the outline of tumour cells (ghost cells) are recognised on H&E
Be careful when using immuno as there are no definite rules.

Use immuno to confirm your suspected diagnosis not to give the initial diagnosis.