Markers of melanocytic tumours

Basic facts
- Antibodies well known to most, for many years
- Well recognized diagnostic situation
- NordiQC experience this far

Discussion

There are several markers, reported to stain positively in melanoma cells and cells of other naevocellular tumours:
- Protein s-100
- Vimentin
- Microphthalmia transcription factor
- Tyrosinase
- HMB 45
- Melan A
- C-kit (CD 117) and many others

Markers of melanocytic tumours

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Protein s-100
- Dimeric 21kDa protein
- Two subunits: α and β
- May be found in the nucleus, the cytoplasm and the cytoplasmic membrane
- Present, for instance, glial tissue, Schwann cells, melanocytes, myoepithelial cells and some glandular epithelium (sweat glands, kidney, breast, striated muscle, chondrocytes and FDC)
Markers of melanocytic tumours

Protein s-100 continued
- Present in >90% of
  - Astrocytoma, gli tumours
  - Benign and malignant Schwannomas, neurofibromas
  - Granular cell tumours
  - Myoepithelial tumours
  - Polymorphous low grade adenocarcinoma
  - Langherhan’s cell histiocytosis, xanthgranulomas
  - Chondromas
  - Lipomas, liposarcomas

Markers of melanocytic tumours

Protein s-100 continued
- Present in >50-90% of
  - PNET
  - Clear cell sarcomas
  - Rhabdomyosarcomas
  - Chondroid tumours
  - Sweat gland carcinomas
  - Renal cell carcinoma
  - Serous and endometroid ovarian tumours
  - Monocytic/monoblastic leukemias

Markers of melanocytic tumours

Protein s-100 continued
- Present in <50% of
  - Granulosa cell tumours
  - Adenocarcinomas of breast
  - Several others

Thus, s-100 is sensitive but very unspecific for melanocytic neoplasms. Protein s-100 may also be of importance in tumour diagnosis not involving melanomas.

Markers of melanocytic tumours

Melanoma-specific antigen (MSA) HMB-45
- Considerably more specific than s-100
- Less sensitive than s-100
- May play a role in rare instances of differential diagnosis in non-melanocytic neoplasms

Markers of melanocytic tumours

Melanoma-specific antigen (MSA) HMB-45
- Present in junction nevi, compound nevi (epidermal part, weaker in dermal part), blue nevi, dysplastic nevi, Spitz
- Rhabdomyoma
- Angiomyolipoma
- Clear cell sarcoma
- and some other fairly uncommon neoplasms and other conditions
Markers of melanocytic tumours

- **Melan A**
  - Also called MART-1 (Melanocyte antigen recognized by T-cells).
  - 20-22 kDa protein associated with endoplasmatic reticulum and melanosomes.
  - Expressed in all normal melanocytes and melanocytic cell-lines.
  - Also detected in steroid-producing cells (adrenal cortex, Leydig cells, granulosa and theca cells) due to cross-reaction since the MART-encoding gene is not detected in these cells.

Markers of melanocytic tumours

- **Melan A**
  - Expressed in 80-100% of melanomas.
  - Almost 100% expression in primary cutaneous and mucosal melanoma.
  - Less often and weaker expressed in metastatic lesions.
  - Desmoplastic melanomas may be negative.

Markers of melanocytic tumours

- **Melan A**
  - Positive in other neoplasms of melanocytic origin, such as:
    - Benign nevi, Spitz, blue nevi.
    - Clear cell sarcoma.
    - Melanotic Schwannoma.
    - PEComa (perivascular epithelioid cell tumour).
    - Angiomyolipoma.
    - Steroid-producing tumours.

Markers of melanocytic tumours

- **Immunohistochemistry using melanocytic markers** is of particular value in the diagnosis in cases of:
  - Cutaneous melanocytic tumours with an unusual appearance:
    - Signet ring cell melanoma.
    - Spindle cell or desmoplastic melanoma.
  - Melanocytic tumours with an unusual localization (and sometimes also an unusual appearance):
    - Nasal.

Markers of melanocytic tumours

- **Immunohistochemistry using melanocytic markers** is of particular value in the diagnosis in cases of:
  - Metastatic lesions with no known primary tumour.
  - To confirm metastatic melanoma/melanocytic tumours - sentinel node.
  - As a help in the distinction between benign and malignant lesions.
Melanoma in rectal mucosa

Metastatic melanoma in duodenum

Metastatic melanoma in duodenum

Melanoma in nasal mucosa

Melanoma in the anal mucosa
Melanoma in the anal mucosa

Malignant melanoma in the maxillary sinus

Metastatic melanoma in the jejunal wall

The NordiQC experience
- Run 7, 2003
- 63 labs submitted s-100 stainings
- 66 labs submitted MSA stainings
- 35 labs submitted Melan A stainings

The NordiQC experience
- Multi-tissue block, s-100 staining
  - Malignant melanoma of the bowel
  - Brain tissue
  - Malignant melanoma of the testis
  - Appendix
  - Blue nevus

The NordiQC experience
- Criteria for the s-100 staining as optimal:
  - Strong and distinct nuclear and cytoplasmic staining reaction in the tumour cells of malignant melanoma and the nevus
  - Glial cells, Schwann cells, fat cells, reticulum cells including epidermal Langerhan’s cells should also be demonstrated.
The NordiQC experience

- Results of the assessment of s-100 stainings
  - Optimal 19 (30%)
  - Good 26 (41%)
  - Borderline 10 (16%)
  - Poor 8 (13%)

The NordiQC experience

- S-100 staining
- What characterized the submitted protocols when the staining results were optimal or good?
  - Polyclonal ab Z0311
  - Sufficient concentration of the ab
  - Sufficient pre-treatment (HIER or enzymatic)

The NordiQC experience, s-100

- Multi-tissue block, MSA staining
  - Malignant melanoma of the bowel
  - Granulosa cell tumour
  - Malignant melanoma of the testis
  - Adrenal gland
  - Blue nevus

The NordiQC experience

- Criteria for the MSA staining as optimal:
  - Strong and distinct cytoplasmic staining reaction in the tumour cells of malignant melanoma and the nevus
  - No staining reaction seen in other cells.

The NordiQC experience

- Results of the assessment of MSA stainings
  - Optimal 30 (45%)
  - Good 19 (29%)
  - Borderline 13 (20%)
  - Poor 4 (6%)
The NordiQC experience

- MSA staining
  - What characterized the submitted protocols when the staining results were optimal or good?
    - Sufficient concentration of the ab
    - Sufficient pre-treatment (HIER or enzymatic)
    - The use of a non-biotin based detection system or efficient biotin blocking

The NordiQC experience

- Multi-tissue block, Melan A staining
  - Malignant melanoma of the bowel
  - Granulosa cell tumour
  - Malignant melanoma of the testis
  - Adrenal gland
  - Blue nevus

The NordiQC experience

- Criteria for assessing the Melan A staining as optimal:
  - Strong and distinct cytoplasmic staining reaction in the normal melanocytes, the tumour cells of malignant melanoma and the nevus
  - If mAb was used, a distinct staining of the granulosa cell tumour and adrenal cortex cells should be seen
  - No staining reaction seen in other cells.

The NordiQC experience

- Results of the assessment of Melan A stainings (35 labs submitting stainings)
  - Optimal 14 (40%)
  - Good 10 (29%)
  - Borderline 8 (23%)
  - Poor 3 (8%)

The NordiQC experience

- Melan A staining
  - What characterized the submitted protocols when the staining results were optimal or good?
    - The use of HIER in Tris-EDTA pH 9, when using mAb A103
    - Sufficient pre-treatment (HIER or enzymatic)
    - Sufficient concentration of the mAb

The NordiQC experience

- Melan A
  - Blue nevus
  - Malignant melanoma
  - Malignant melanoma
  - Granulosa cell tumour
  - Adrenal cortex

A. Blue nevus
B. Malignant melanoma
C. Malignant melanoma
D. Granulosa cell tumour
E. Adrenal cortex
What can be suggested or concluded?

Suggestions/conclusions I

- The antibody panel for melanocytic differentiation should contain:
  - Protein s-100 for its sensitivity
  - Melan A for its specificity

- In fact, a tumour cell population that is s-100+/Mel A+ is very likely to be melanocytic.

Suggestions/conclusions II

- The antibody panel for melanocytic differentiation may also contain:
  - Microphthalmia transcription factor
  - A nuclear marker
  - Expressed in desmoplastic variants
  - When appropriate:
    - Vimentin always positive in melanoma
    - Ki67 may contribute in some cases

Suggestions/conclusions III

- The NordQC experience clearly indicates that improvements are needed and that external quality control is very important in immunohistochemistry to achieve and maintain high standards in routine diagnostic work.

Thanks for listening.