Case Studies Illustrating the Contribution of Cytogenetics to Anatomic Pathology

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Jan 22, 2013
Outline

- Role of the Pathologist
  - Historical
  - Molecular pathology (MP)
    - Concepts: Toteomics / personalized medicine
      - EX: Pharmacogenetics / Pharmacogenomics
- Game changers
  - Better understanding of biology
    - Examples: Colon, Breast, Lung, Melanoma
- Technological advances
- Clinical trials
  - Cooperative group
  - Non-cooperative group
- Case Studies
  - 30M neck mass NUTMC
  - 10F UR tract mass mSS
  - 8F serratus mass MOABCNF
  - 22F kidney Renal MA
  - 72M sciatic nerve eMPNST
Molecular Pathology

- Concepts:
  - “Toteomics”
    - Genomics (genes)
      - DNA, RNA (transcriptome)
    - Proteomics
      - Tissue-based
      - Plasma
    - Epigenetics
      - miRNA
    - Metabolomics
    - Cytomics (single cell level)

- Concepts:
  - Personalized Medicine
    - Personalized medicine is a medical model proposing the customization of healthcare, with all decisions and practices being tailored to the individual patient by use of genetic or other information (Ref: Wikipedia, 2012)
Contribution of Genetics

- Many levels:
  - Diagnosis: WHO Classification of tumors (examples)
    - “AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1” (2008)
    - “Carcinoma with t(15;19)” (2004)
  - Prognosis
    - Complex karyotype often associated with poor prognosis
  - Therapeutics / Targeted Therapies
  - Biology
  - Non-specific
    - “laundry list”, telomeric shortening and chromosomal instability
**Case: 30M neck mass (IRAPNUTMC)**

- **HPI:** 30 y/o caucasian male with non-healing lesion involving left molar/submandibular region
- **PMHx/PSHx:** non-contributory; no FamHx cancer
- **PE:**
  - **HEENT:** erythematous left oral mucosa near molar teeth with punctate ulceration; palpable swelling of left submandibular soft tissue
  - **All other systems unremarkable**
- **A biopsy was performed**
**Left neck mass biopsy (OSH)**

OSH Diagnosis: “Germ cell tumor consistent with seminoma”

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<tr>
<th>IHC Summary</th>
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<tr>
<td><strong>POSITIVE</strong></td>
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<td>PLAP (focal)</td>
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<td>βhCG</td>
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<td>CD30</td>
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<td>S100</td>
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<td>MPO</td>
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<td>CD4</td>
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<td>EBV</td>
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Clinical History – Treatment Course

- Radiologic workup revealed widespread visceral and bony metastases
- 3 cycles of BEP chemotherapy plus palliative radiation of spine without tumor response
- Transferred to ALGH
- Submandibular tumor rapidly progressed to a fungating, MRSA-infected mass
- Hospice care was initiated and autopsy obtained
Ancillary Studies

IHC Summary

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<th>POSITIVE</th>
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<tr>
<td>p63 (strong, diffuse)</td>
<td>PLAP</td>
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<tr>
<td>CK7 (focal)</td>
<td>AFP</td>
</tr>
<tr>
<td>CAM5.2 (focal)</td>
<td>βhCG</td>
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<td>NUT protein (BWH, Boston)</td>
<td>Myogenin</td>
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<td>Synaptophysin</td>
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<td></td>
<td>Desmin</td>
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<td>CD45</td>
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<td>MAK-6</td>
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- Cytogenetics – Fresh tumor:
  - Neck tumor (6/22/12)
  - Neck tumor (autopsy)
  - Liver metastasis (autopsy)
  - Pleural metastasis (autopsy)
Cytogenetics – Fresh tumor:
- Neck tumor (6/22/12)
- Neck tumor (autopsy)
- Liver metastasis (autopsy)
- Pleural metastasis (autopsy)

49,XY,add(1)(q42),der(2)t(2;3)(q33;p21),t(3;6)(p21;p23),+6,+8,der(8)
t(3;8)(p21;p23),+12, del(12)(p11.2),t(15;19)(q14;p13.3)[11]/49,
idem,der(7)t(4;7)(q31.1;q32)[2]/46,XY[7]
**NUT Midline Carcinoma**

- Highly aggressive undifferentiated malignancy occurring primarily in the head, neck, and mediastinum
  - May mimic germ cell tumor
- Defined by rearrangement of \textit{NUT} on chromosome 15
- Thought to be distinctive genetic variant of squamous cell carcinoma or undifferentiated tumor arising from common squamous precursor
- Average survival is 6.7 months from time of diagnosis

Contribution of Genetics - NUT carcinoma case

- Many levels:
  > **Diagnosis**: WHO Classification of tumors (examples)
    > “Carcinoma with t(15;19)” (2004)
  > **Prognosis**
    > Complex karyotype often associated with poor prognosis
  > **Therapeutics / Targeted Therapies**
  > **Biology**:
    > Cell lines distributed to researchers
  > **Non-specific**
    > “laundry list”, telomeric shortening and chromosomal instability
Case: 10F UR tract mass (mSS)

- 10 year-old female presented with upper airway obstruction / right neck mass
- Large mass bled profusely at time of biopsy
- Pathology given 0.6 cm aggregate of partly necrotic tissue
  > Frozen section: “That’s all you are going to get”

- Pieces (6 mm) of tissue (LS10-6751):
  - Frozen section
  - Flow cytometry for lymphoma (fresh tissue)
  - Karyotype (fresh tissue)
  - Immunohistochemistry (FFPE)
  - FISH (FFPE)
Case Study – J.T.

- Small blue cell tumor:
  - Lymphoma
  - Sarcoma
    - Ewings / PNET
    - Rhabdomyosarcoma
    - Synovial sarcoma
    - Other
  - Melanoma
  - Poorly differentiated carcinoma
  - Other…
Case Study – J.T.

- 6 mm piece of tissue:
  - Flow cytometry
    - Negative for lymphoma
  - Immunohistochemistry:
    - Suggestive of Ewings (atypical)/ PNET but SS can be Fli-1 (20%) and CD99 (63%) positive
    - Too little tissue for TLE1, p-4EBP1, CK7, etc
  - FISH:
    - Nuc ish 22q12(EWSR1x2) - Negative
  - Karyotype
    - pending
Seven days post biopsy

46,XX,t(X;18)(p11.2;q11.2)[20]
Contribution of Genetics – monophasic synovial sarcoma case

Many levels:

- Diagnosis: WHO Classification of tumors
- Prognosis
  - Complex karyotype often associated with poor prognosis
- Therapeutics / Targeted Therapies
- Biology
- Non-specific
  - “laundry list”, telomeric shortening and chromosomal instability
Case: 8F serratus mass (MOABCNF)

- HPI: 8 y/o F with progressively enlarging, well-circumscribed, 5 cm mass in right anterior chest wall at least focally, intimately associated with serratus anterior muscles
- PMHx/PSHx:
  - non-contributory
  - no history of trauma given
- XRT:
  - Not available; no classic zonal ossification?
- PE: Essentially negative
- An excision was performed
Case Study – K.L

- Central
- Intermediate
- ABC-like
Differential diagnosis

- **Myositis ossificans**, but our case...
  - lacks central NF-like → transition → osteoid zonation

- **Fibro-osseous pseudotumor of digits**, but our case is...
  - not digital and lacks central osteoid → peripheral spindle cell zonation

- **Extraskeletal osteosarcoma**, but our case is...
  - wrong age and shows minimal atypia

- **Proliferative fasciitis**, but our case has...
  - too much osteoid and no plump ganglion-like fibroblast

- **Periostitis or exuberant fracture callus**, but our case is...
  - not associated with bone

- **Nodular fasciitis (NF)**

- **Soft tissue aneurysmal bone cyst (ABC)**
46,XX,t(9;17)(q22;p13)[9]/46,XX[12]
Myositis ossificans genetics:

MO-NF-ABC related? Consider . . .

- **Morphology:**
  - The central zone and early phase of MO (which rarely gets excised) looks like NF
  - Metaplastic bone in NF:
    - May be focal or extensive (ossifying fasciitis; lacks zonation)

- **Genetics:**
  - NF genetics: reported 3q21, t(2;15), -2, -13, 15 (NTRK3): 44 of 48 (92%) had \textit{USP6} rearrangements (Erickson-Johnson MR, et al. \textit{Lab Invest} 2011:91:1427 by PCR)
  - ABC (of bone) genetics: 22 of 35 (63%) with 17p13 (\textit{USP6}) abnormalities (Althof PA, et al. \textit{Modern Pathol} 2004:17:518 by cytogenetics and FISH)
Contribution of Genetics to MONFABC case

- Many levels:
  - Diagnosis: WHO Classification of tumors
  - Prognosis
    - Complex karyotype often associated with poor prognosis
  - Therapeutics / Targeted Therapies
  - Biology
    - This case supports the concept that MO-NF-ABC are related, possibly through *USP6*
    - “MONFstABaComa: Report of a case and review of the literature”
  - Non-specific
    - “laundry list”, telomeric shortening and chromosomal instability
Case: 22F kidney (RMA)

- HPI: 22 y/o F with Crohn’s disease found to have 2 cm cortical-based right renal mass
- PMHx/PSHx:
  > non-contributory
- XRT:
  > Non-contributory
- PE: Essentially negative
- Partial nephrectomy performed
No gross available
<table>
<thead>
<tr>
<th>Histotype</th>
<th>Cytogenetics</th>
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<tbody>
<tr>
<td>Clear Cell</td>
<td>-3p</td>
</tr>
<tr>
<td>Papillary</td>
<td>+7, +17, -Y (sex chromo. loss)</td>
</tr>
<tr>
<td>Chromophobe</td>
<td>Nonspecific (-1p, -2p, -6p, -10p, -13p, -17p, -21q)</td>
</tr>
<tr>
<td>Mucinous tubular and spindle cell carcinoma</td>
<td>-1,4,6,8,9,13,14,15,22</td>
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<tr>
<td>Oncocytoma</td>
<td>-1, -Y</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>Not reported</td>
</tr>
<tr>
<td>Collecting duct</td>
<td>Isolated case reports (del[1q32.1-32.2], -8p, -13q, others)</td>
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“The authors believe that better genetic understanding of tumorigenesis and its relation to the tumor phenotype will provide the best prognostic information.”

Future Prognostic Factors in Renal Cell Carcinoma:
Workgroup No. 5.,
Papillary Renal Cell Carcinoma - Prognosis.

Papillary adenoma?

- +7p, +17p, -Y
- > 0.5 cm. (WHO)

Indolent papillary RCC

- Topoisomerase IIα*
  - +12, +16, +20

Papillary RCC, type 2

Locally aggressive papillary RCC

- LOH 9p13

Metastatic papillary RCC
Oncocytoma (intercalating cell adenoma) \(\rightarrow\) Chromophobe RCC (intercalating cell carcinoma)?

Intercalating cell adenoma (oncocytoma?)

Intercalating cells

-1, -Y

BHD gene?

"Hybrid Tumors"

"Hybrid Tumors"

Telomerase shortening*

-1,-2,-6,-10,-13,-17,-21,-Y

-3p

Intercalating cell carcinoma

(Chromophobe RCC?)

? Chromophobe with sarcomatoid

RCC translocation tumors – t(6;11) (different case)
Renal metanephric adenoma

- Genetics of metanephric adenoma:
  - WT1 family of tumors?
  - t(9;15)(p24;q24) and inv(12)(q13,q15) (Rakheja D, et al *Ped Develop Pathol* 2005;8:218)
46,XX,t(9;15)(p24;q24)[20]
Contribution of Genetics to renal metanephric adenoma

- Many levels:
  - Diagnosis: WHO Classification of tumors (examples)
  - Prognosis
    - Complex karyotype often associated with poor prognosis
  - Therapeutics / Targeted Therapies
  - Biology
    - Second case of renal MA with t(9;15)(p24;q24)
    - KANK1? Narrowed down to 170kb pair region using FISH probes
    - Sequencing?
  - Non-specific
    - “laundry list”, telomeric shortening and chromosomal instability
Case: 72M sciatic nerve (eMPNST)

- HPI: 72 y/o M left leg weakness over several months found to have sciatic nerve mass
- PMHx/PSHx:
  - non-contributory
- XRT:
  - Pseudoencapsulated 12 cm, fusiform tumor
- PE: Essentially negative
- Excisional biopsies performed
Case Study – P.P.

CD57 (1+), CK7, MART-1, MITF, and EMA (-)
MPNST and epithelioid variant of MPNST

- Genetics of MPNST:
  > 17q11.2 (NF1), 7p, 5p, 8q, 12q, 9p (CDKN2), 13q, 1p

- Genetics of epithelioid variant of MPNST:
46,XY, del (5p)[20]
Contribution of Genetics to epithelioid MPNST case

- Many levels:
  - Diagnosis: WHO Classification of tumors (examples)
  - Prognosis
    - Complex karyotype often associated with poor prognosis
  - Therapeutics / Targeted Therapies
  - Biology
    - del(5p) specific for epithelioid variant?
  - Non-specific?
    - “laundry list”, telomeric shortening and chromosomal instability
Current Menu

- **Oncology**
  - EGFR, KRAS, BRAF, BCR/ABL (Q), JAK2 (Q), B/T cell clonality, MLH1 methylation

- **Infectious Diseases**
  - VIRAL – Respiratory viral panel (Luminex; GenProbe), HCV, HBV, VZV, HSV, CMV, BKV, EBV, enterovirus; HIV/HCV genotyping
  - BACTERIAL – MRSA, C diff, KPC, BP/BPP, mycoplasma, legionella, chlamydia

- **Genetics**
  - MSI, CF, Factor 5 Leiden, Factor 2, MTHFR, hemochromatosis

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