MDM2 IN SOFT TISSUE AND BONE SARCOMAS

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WHAT IS MDM2?
(MDM TWOMICS)

MDM2 IN SARCOMAS?
(MDM TWOMAS)

MDM2MICS?

- Murine Double Minute clone 2: oncogene in double minutes of spontaneously transformed mouse fibroblasts
- 12q15
- Controls/blocks p53 activity:
  - p53: nucleus → cytoplasm, ubiquitination
  - inhibits p53 transactivation domain

NO CONFLICT OF INTERESTS
MDM2MICS?
- MDM2 amplification/overexpression for cancer cells is an elegant means to block p53
- 7% of human cancers show MDM2 amplification
- Molecules that block the MDM2-p53 interaction can reestablish wild type p53 activity

MDM2MAS?
- Atypical lipomatous tumor/well differentiated liposarcoma
- Dedifferentiated liposarcoma
- Intimal sarcoma
- Low grade osteosarcoma (parosteal/intramedullary)

ATYPICAL LIPOMATOUS TUMOR/WELL DIFFERENTIATED LIPOSARCOMA
- Synonyms
- 40-45% liposarcoma
- Middle-aged adults, extremities (deep) > retroperitoneum, paratesticulum, mediastinum
- Variation adipocyte size/hyperchromatic/atypical nuclei/lipoblasts (+/-)
- Lipoma-like/sclerosing/inflammatory
- Prognosis: extremities >>> retroperitoneum
ATYPICAL LIPOMATOUS TUMOR/WELL DIFFERENTIATED LIPOSARCOMA

- Giant markers/supernumerary ring chromosomes: 12q13-15
- Amplification of MDM2, CDK4, HMG-A2, GLI1…
- FISH to detect MDM2 amplification is very useful
- Cave MDM2 immunohistochemistry:
  * focal to negative
  * nuclear
  * macrophages often false +
- MDM2/CDK4/p16 immuno: sensitivity ↑*

Well differentiated fatty tumor

FISH test for MDM2 recommended
- Recurrent lesion
- Deep extremity lesion >10 cm, pt > 50 years
-equivocal atypia
- Retroperitoneum/abdomen/pelvis
- None of the above criteria but worrisome clinical/radiological features

FISH test for MDM2 not recommended
- Superficial location
- Hands/feet

CD68

FISH probes: MDM2-5Q (red) + CEP12-5G (green) as a reference probe (covering centromeric region of chromosome 12)

DEDIFFERENTIATED LIPOSARCOMA

- Transition of WDL/ALT towards a nonlipogenic sarcoma in 1st tumor or recurrence
- The well differentiated component may be lacking
- 90% de novo, +/- 10% of WDL/ALT dedifferentiate
- Retroperitoneum (80%) > extremities
  - most frequent retroperitoneal sarcoma
  - extremity undifferentiated pleomorphic sarcoma
  - with MDM2 amplification = dediff. Liposarca*


DEDIFFERENTIATED LIPOSARCOMA

- Giant markers/supernumerary ring chromosomes: 12q13-15 (MDM2, CDK4, HMGA2…)
- MDM2 immuno usually strongly +
- 6p23, 1p32 (JUN) co-amplification


- Usually looks like a high grade spindle/pleomorphic sarcoma
-…but also: myxoid, low grade looking, heterologous differentiation (chondro-, osteo-, myogenic…)
- Recurrence ≥ 40%
- Metastasis: 15-30%
- Correlation between grade and outcome?*

Male, 83 yrs, retroperitoneal tumor (26 cm)...
Female, 58 yrs, retroperitoneal tumor...

...died 5 yrs after resection (inoperable recurrence)
Male, 52 yrs, tumor lower pole kidney: punction biopsy
MDM2 FISH probes: MDM2-SO (red) + CEP12-SG (green) as a reference probe (covering centromeric region of chromosome 12)
INTIMAL SARCOMA

- Very rare, adults with broad age range
- Wall of large blood vessels, proximal pulmonary arteries most frequent
- Most frequent primary cardiac sarcoma*
- Very poor prognosis (embolic dissemination)
- Histology very heterogeneous: spindly/anaplastic/myxoid/sclerotic/osteoid…
  → any weird looking intraluminal sarcoma: think intimal sarcoma!


INTIMAL SARCOMA

- Amplification of 12q12-15: MDM2/CDK4
- Amplification/activation of PDGFRα/KIT (4q12) and EGFR (7p11)

*Cuppens et J Thorac Oncol 2014;9:897-899
Boy, 4 yrs, tumor left ventricle
PAROSTEAL OSTEOSARCOMA

- 4-5% of osteosarcoma, most frequent surface osteosarcoma
- Peak incidence in 3rd decade, slight female predominance
- 70% posterior surface of distal femur, tibia, humerus also rarely involved

PAROSTEAL OSTEOSARCOMA

- Looks often benign. Fascicles of non-atypical spindle cells admixed with parallel bone trabeculae, +/- osteoblastic rimming. 50%: cartilage islands
- MDM2 and CDK4 expression/amplification by immuno/FISH
- Complete resection: 5 yr survival 91%. No chemotherapy, unless dedifferentiated (15-20%), then prognosis as in conventional type.
male, 14 yrs, increasing problems with knee flexion...
Female, 19 yrs, slowly increasing pain in shoulder since 6 months, and palpable mass…

...resection, after 3 yrs recurrence?
Male, 24 yrs, car accident 4 yrs ago, knee pain since then, recently increasing pain and swelling above the knee, biopsy and resection...
dedifferentiation...
LOW GRADE CENTRAL OSTEOSARCOMA

- 1-2% of osteosarcoma
- 50% in 2nd-3rd decade
- Long bones lower extremity, mainly distal femur and proximal tibia
- Fascicular moderately cellular fibroblastic proliferation with minimal/no atypia
- Curved bone trabeculae (fibrous dysplasia-like) or long longitudinal seams of bone (parosteal osteosarcoma-like)

LOW GRADE CENTRAL OSTEOSARCOMA

- Permeation of pre-existing bone or soft tissue extension may be only clue for malignancy
- MDM2 and CDK4 expression/amplification by immuno/FISH
- Upon resection 5 yr survival = 90% Chemotherapy only in cases with progression to high grade osteosarcoma (10-36%)
FISH: MDM2 + CEP12 (Kreatech)
CONCLUSIONS

M eaningful, molecular mechanism

D iagnostic, FISH > Immuno

M aybe drugable

2 make the life of a pathologist easier…