Case 4

Molecular Pathology and Trainees: Next generation pathology

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Disclosure Information

• I have no conflict of interest.
Case 4 - Patient's history

• 54/M
• 7 month history of scrotal swelling

• Physical examination: 5 cm mass in right inguinal region
• Medical history: Diabetes mellitus and ischemic heart disease
• Right inguinal orchiectomy
Case 4 - Macroscopic examination

• 7,5x5,5x5 cm tumor in spermatic cord

• Cross-sections:
  - Multinodular solid mass
  - Tan-gray and yellow-tan colors
  - Focal hemorrhagies
Case 4 - Microscopic examination
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• Criteria for identifying lipoblasts include:
  - A hyperchromatic indented or sharply scalloped nucleus
  - Lipid-rich droplets in the cytoplasm (mono or multivacuolated)
  - Appropriate histologic background

Sarcoma infiltrating fat? Lipoblast?
Case 4 – Differential diagnoses

- A sarcoma was suspected. FNCLCC grade 2
  - Tumor differentiation: Score 3
  - Mitotic count: 6/10 HPF
  - Necrosis: 10%

- Undifferentiated pleomorphic sarcoma
  - Pleomorphic liposarcoma
  - Dedifferentiated liposarcoma (DDLS)
  - Pleomorphic leiomyosarcoma
  - Pleomorphic rhabdomyosarcoma
Undifferentiated pleomorphic sarcoma

- No specific line of differentiation
- **Lacks** atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDL) areas
- Desmin and H-Caldesmon are typically negative\(^1\).
- Immunoprofile “**Vimentin only**”
Pleomorphic liposarcoma

• High grade sarcoma containing pleomorphic lipoblasts (presence of lipoblasts is necessary for diagnosis)\(^{(2)}\)

• No ALT/WDL component

• MDM2 and CDK4 are mostly negative\(^{(3)}\)
Pleomorphic leiomyosarcoma

Low grade area at least focally with a fascicular arrangement and elongated cells with blunt-ended nuclei and a perinuclear vacuole\(^{(1)}\)

- H-Caldesmon (+)
- Smooth Muscle Actin (SMA) (+)
- Muscle Specific Actin (MSA) (+)
- Desmin (+)

Short intersecting fascicles
Pleomorphic rhabdomyosarcoma

- Large cells with eosinophilic cytoplasm, eccentric vesicular nuclei and prominent nucleoli\(^1\)
  - Desmin (+)
  - Myogenin (+)
  - MyoD1 (+)

Rhabdomyoblasts:
  - Dedifferentiated chondrosarcoma
  - Dedifferentiated liposarcoma

Spindle-shaped cells and large cells with eosinophilic cytoplasm
Results of specific further investigations - IHC

- In pleomorphic areas:
  - Desmin (+)
  - H-Caldesmon (+)
  - SMA (Focal) (+)
  - Ki-67 proliferation index: %35

- MSA (-)
- Myogenin (-)
- MyoD1 (-)
- S100 (-)
- CD34 (-)
- CDK4 (+)
Results of specific further investigations-IHC
Results of specific further investigations - IHC
FISH for MDM2/CCP12
Final diagnosis:

Dedifferentiated liposarcoma
Follow-up

• No infiltration in the testis
• Soft tissue surgical margins - focally positive
• 6 rounds of chemotherapy of doxorubicin and ifosfamide
• Adjuvant radiotherapy
• 1-year follow up: FDG-PET no relapse or metastasis
Discussion

• Paratesticular area: Ductus deferens, tunica vaginalis, spermatic cord and other supportive tissues (fat, ligament, muscle) of the testis\(^{(4)}\)

• Sarcoma <5% of all scrotal masses\(^{(5)}\)

• Most common types: Liposarcoma, leiomyosarcoma, rhabdomyosarcoma, undifferentiated pleomorphic sarcoma and fibrosarcoma\(^{(4)}\)
Discussion

• WDL: Irregular fibrous bands, marked variation in adipocyte size, enlarged hyperchromatic stromal cells and occasional lipoblasts.

• Subset of WDL progresses to DDLS

• In 1979, Evans described DDLS, as a "non-lipogenic" sarcoma alongside with an ALT/WDL\(^5\).
Discussion

• DDLS – High grade / low grade

• Interface between well-differentiated and dedifferentiated areas can be abrupt, gradual and occasionally in a mosaic pattern\(^5\).

• Heterologous dedifferentiations:
  - Meningothelial-like whorling
  - Metaplastic bone formation
  - Rhabdomyosarcomatous differentiation
  - Myogenic/myofibroblastic dif.

• Homologous differentiation
  - Lipoblasts within the dedifferentiated component
Discussion

• Immunohistochemistry (IHC) for MDM2 and CDK4 are almost invariably positive in liposarcomas\(^3\).
Discussion

• Giant marker and supernumary ring chromosomes contain amplified sequences of 12q13-15\(^{(1)}\)

• MDM2 is consistently amplified as a result of this abnormality.

• CDK4 is co-amplified with MDM2 in about 90% of cases.
Discussion

- Amplification of MDM2 and CDK4 inhibits apoptosis and increase cell proliferation\(^{(1)}\)
- Overexpression of MDM2 protein inactivates p53\(^{(3)}\)
- CDK4 phosphorylates the RB1 gene allowing the cell cycle to escape the G1-S checkpoint\(^{(8)}\)
Conclusion

• More indolent than UPS and pleomorphic liposarcoma/leiomyosarcoma\textsuperscript{(3, 9)}

• Site - most significant prognostic factor

• Firstline treatment – surgery

-Retroperitoneum and spermatic cord – impossible to obtain a wide excision margin - local recurrence
Conclusion

• To achieve accurate diagnosis, we should conjunct immunohistochemistry and molecular techniques with the morphological evidences of specific differentiation.
References:


Thank you

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