Molecular Diagnosis of Soft Tissue Tumors: Avoid Pitfalls

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Overview

I. When should we rely on the help of molecular testing?

II. Specificity, Prevalence, and Prognostic Implications of Molecular Abnormalities.

III. ‘Gold Standard’ in surgical pathology of soft tissue tumors
I. When should we rely on the help of molecular testing?

- difficult distinctions between a benign and malignant diagnosis
- unusual morphologic features
- unusual clinical presentations or unexpected immunohistochemical results
- refined classification may directly impact on clinical management of the patient
- confirm diagnosis in conflicting second opinions
Benign vs Malignant STT

- Perineurioma versus Low Grade Fibromyxoid Sarcoma
- SFT/HPC versus Synovial Sarcoma (SS)
- Angiomatoid Fibrous Histiocytoma vs sarcoma
- Lipoblastoma vs myxoid liposarcoma in children
Sarcomas with unusual morphologic appearance

- Desmoplastic Round Cell Tumor (DRCT) with predominantly rosettes or tubular structure formation

- Small cell GIST in children
STT with typical morphology but unusual clinical presentation

- Ewing Sarcoma in superficial location
- Ewing Sarcoma in older individuals (>40 years)
- Ewing Sarcoma in visceral location
STT associated with an unusual immunoprofile

– Ewing Sarcoma (ES) with strong Keratin expression

– Synovial sarcoma with S100 protein positivity
Refined classification may directly impact on clinical management

– GIST versus sarcoma, NOS
– Ewing Sarcoma vs Poorly differentiated Synovial Sarcoma
– ARMS vs ERMS
Refinement in diagnosis impacts on outcome or clinical follow-up

– Liposarcoma with extensive myxoid changes in the retroperitoneum

– HG sarcomas of the extremities: dedifferentiated liposarcoma vs MFH
Confirming diagnosis when in disagreement with other expert review

- Disprove a diagnosis of Synovial Sarcoma in an MPNST
- Confirm a certain sarcoma subtype (ARMS vs ERMS)
Applying Molecular Diagnosis in Other Clinical Scenarios

- Establish a primary diagnosis of sarcoma versus metastatic disease
  - Primary GI clear cell sarcoma vs metastatic melanoma to the gut
Applying Molecular Diagnosis

• In cases with discordant results between morphology and cytogenetic results:
  – Pediatric tumor with an *EWSR1* gene rearrangement does not always equal an Ewing sarcoma
  • Angiomatoid Fibrous Histiocytoma (AFH)
  • Myoepithelioma (ME)
II. Specificity, Prevalence, and Prognostic Implications of Molecular Abnormalities

• Fusion transcripts have been proved not only to be highly specific molecular diagnostic markers, but their prevalence in most sarcomas is such that they come to define these entities.

• The molecular heterogeneity of fusion transcripts has been suggested to have a prognostic role in certain sarcoma types (Ewing sarcoma, ARMS)
Caveats of wide-availability of certain genetic tests

- are now being applied on archival material, in Academic Institutions or Private labs, lacking appropriate sarcoma pathology expert review:
- FISH test is looking at one partner at the time
  - Promiscuity of certain translocation partners: EWSR1 gene family of tumors (ES, DRCT, ExMyxCS, MLS, CCS, GI CCS, AFH, ...ME, ...?).
- Diagnostic pitfalls triggered by misinterpretations of gene rearrangements results, with automatic classification in major translocation-positive sarcomas
III. ‘Gold Standard’ in surgical pathology of soft tissue tumors

• In most cases molecular results should be used as validation of the morphologic differential diagnosis, corroborated with immunohistochemical findings and clinical information, rather than a challenge to the supremacy of histopathology.