Is Formalin-Fixed Paraffin Embedded Tissue Good Enough for Studies of Transmission Electron Microscopy of Tumors? A Comparative Study with Wet Tissue

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Abstract

Transmission electron microscopy (TEM) has historically been pivotal in the diagnosis of neoplasms with challenging histopathology. However, its routine use has declined due to associated costs and the advent of ancillary techniques such as immunohistochemistry. This study compares the diagnostic utility of formalin-fixed paraffin-embedded (FFPE) tissue versus wet glutaraldehyde-paraformaldehyde-fixed tissue (WT) for TEM in neoplastic lesions. A retrospective analysis of 746 cases was performed. Diagnostic utility was assessed based on ultrastructural preservation and concordance with histopathological reports. Key ultrastructural features were identifiable in both cohorts, despite the presence of processing artifacts in FFPE samples. Fisher's exact test revealed no significant difference in diagnostic utility between the two groups. This study challenges the traditional notion that paraffin embedding severely compromises the diagnostic value of TEM. Furthermore, FFPE allows for the precise, targeted sampling of archived tissues, thereby expanding the applicability of TEM in retrospective studies.

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CASES

Case 1: A 17-year-old male with a recent history of pulmonary adenocarcinoma and a significant family history of malignancies (osteosarcoma, liposarcoma, astrocytoma; pending genetics evaluation) presented for a second opinion. A thigh soft tissue core needle biopsy revealed a bland spindle cell neoplasm arranged in a fascicular pattern. The cells featured dense eosinophilic cytoplasm and paracentral nuclei, without cytologic atypia. Immunohistochemical profiling revealed muscle differentiation, showing positivity for desmin, myogenin, and MyoD1. Ultrastructural findings revealed abundant glycogen, small and sparse mitochondria, and Z-bands, establishing the diagnosis of rhabdomyoma. Subsequently, resection of a second lesion from the chest wall demonstrated histopathological features identical to those of the thigh lesion, consistent with multifocal rhabdomyoma. Ultimately, next-generation sequencing (NGS) confirmed the diagnosis of Li-Fraumeni syndrome.

Case 2: A 30 year-old male initiated symptoms a year before with pain in the right foot, that increased 10 weeks before admission. Physical examination disclosed two exophytic ulcerated tomors in 1st and 4th toes. X-ray showed generalized decrease in osseous density and lytic multifocal lessions in astragalus, sphenoid, cuneiform, talus and phalanges. Histologically the tumor composed of plump fusiform cell with rhabdoid features positive for keratin, CD31, ERG and FOS-B. Ultrastrucure revealed abundant Weibel Palade rods. The diagnosis is Pseudomyogenic Hemangioendothelioma, a recently described and OMS recognized entity that is characteristically multicentric, involves several planes of an extremity and has endotelial phenotype with alteration of FOS-B gene. It is locally aggresive and rarely metastatizes. The ultrastructural features are not described in previous publications.

Case 3: A 58-year-old male presented with bilateral cervical lymphadenopathy and exertional dyspnea. Lymph node biopsy revealed a solid, epithelial-appearing malignancy. Initial IHC (CK7+/CK19+; CK20-/NKX3.1-/Napsin A-/TTF-1-) was inconclusive. Subsequent CT imaging suggested pulmonary adenocarcinoma versus mesothelioma. Despite an expanded, non-diagnostic IHC panel (GATA3+; nonspecific WT1/CK5/6; Calretinin-/D2-40-), ultrastructural examination by electron microscopy definitively established the diagnosis of mesotelioma.

Case 4: A 31 year-old male was admitted with refractory headache and neurological symptoma of sudden onset. MRI revealed a well delimited tumor atteched to dura (falcis) and compressing left lobule, the initial diagnosis was o a meningioma and the tumor was resected in multiple fragments. Histologically disclosed poligonal cell with ample pale cytoplasm and reniform nuclei with abundant mitoses. The cell were positive for CD163, S-100, CD1a and Langhrin. Ultrastructure Birbeck granules were found. The diagnosis is Langherhans-cell sarcoma. LCS rarely affects meninges and the appearance is of an infiltrating tumor. Resemblance of LCS with meningioma is nnot described in the literatura. The differential diagnosis in this case includes menningioma, Rosai Dorfman disease and LC Histiocytosis, but a malignant tumor was not considered.