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ORIGINAL ARTICLE

Myxoid liposarcoma: Fine-needle aspiration cytopathology in the molecular era. A report of 24 cases

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KEYWORDS
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Introduction Application of fine-needle aspiration (FNA) biopsy to soft tissue tumors remains underutilized in North America. Myxoid liposarcoma (LPS), the second most common subtype of LPS, is characterized primarily by t(12;16)(q13;p11) which is amenable to FISH analysis using a break-apart probe for *DDIT3*. Little is known regarding FISH testing for *DDIT3* on cytologic specimens. We report our FNA experience with myxoid LPS and application of this molecular probe.

Materials and methods Specimens retrieved from our cytology database used search codes for myxoid LPS. Tissue files were searched for any cases with corresponding FNA biopsies. FNA biopsy was performed using a standard technique.

Results From 24 FNA cases of myxoid LPS (mean age = 52 years), a specific diagnosis was made in 87.5%. Two cases were diagnosed as spindle/round cell neoplasm, and 1 as suspicious for myxoid LPS. There were 2 false positive diagnoses and no false negatives. Nearly all cases arose in the extremities; thigh being most common. Principal cytologic features consisted of discrete myxocellular microfragments, a plexiform capillary pattern, and variable number of univacuolated lipoblasts. Uniformly banal ovoid nuclei were randomly scattered within myxocellular microfragments. FISH analysis for *DDIT3* rearrangement from unstained smears and/or cell-block was positive in 13 cases, and unsuccessful in 3, with no false positive/false negative results.

Conclusion Myxoid LPS is diagnosable in a high percentage of cases using FNA biopsy alone. Confirmatory FISH analysis for *DDIT3* is not only possible, but also valuable for correctly recognizing this neoplasm.

Introduction

Part of the future value of fine-needle aspiration (FNA) cytopathology consists of an ongoing validation of its advantages, limitations, and application to developments in the genetic and molecular understanding of neoplasms.

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Genetically, sarcomas are subdivided into those that are more or less genetically simple and those that are genetically complex. Among the former are Ewing sarcoma, synovial sarcoma, alveolar rhabdomyosarcoma, and myxoid liposarcoma (LPS). Translocations t(12;16)(q13;p11) and t(12;22)(q13;q12) represent *FUS-DDIT3* (90%-95% of cases) and *EWSR1-DDIT3* (5%-10% of cases) gene fusions, respectively, that are unique to and demonstrable in virtually all examples of myxoid LPS.[1]

Prior studies of myxoid LPS have emphasized its major cytomorphologic features.[2-6] Nevertheless, with the exception of a rare case report[7] we are not aware of any series that has utilized the *DDIT3* probe by fluorescence in situ hybridization (FISH) to aspirates of myxoid LPS. Though Klijanienko et al reported that t(12;16)(q13;p11) translocation was detected by cytogenetic analysis in 9 of 11 cases, they provide no other details, and it is unclear from their paper if the FISH probe for *DDIT3* was used.[2] Our aim was to review our FNA examples of myxoid LPS and application of *DDIT3* testing to this neoplasm.

Materials and methods

We reviewed our cytology files for all cases diagnosed as myxoid LPS. In addition, our surgical pathology files were searched for any cases of myxoid LPS that had corresponding cytology specimens.

Percutaneous FNA biopsy was performed on soft tissue mass lesions using standard technique with 21- or 22-gauge needles without image guidance. Typically, 3 to 4 passes were made into each lesion, and each needle pass was rinsed into RPMI-1640 balanced salt solution after expelling material onto glass slides to create conventional smears. No liquid-based slides were made. All smears were air-dried. Immediate assessment using a Romanowsky stain was made in about half the slides. Subsequent Papanicolaou staining was performed on remaining slides after re-hydration and alcohol fixation. When performed, formalin-fixed, paraffin-embedded cell-block (CB) sections were made using the plasma thrombin technique and stained with hematoxylin and eosin. Immunohistochemical (IHC) staining of CB used a standard heat-induced epitope retrieval methodology and commercially available antibodies.

All cases had immediate assessment for adequacy performed by an attending cytopathologist; one of us (PEW) performed the FNA biopsy and issued the final diagnosis in all but three cases. Based on the judgment of the examining pathologist, a subset of cases had a single unstained slide sent for interphase FISH analysis after examining Romanowsky-stained smears. In other cases, a CB alone or CB plus a single unstained smear were analyzed by FISH using a commercially available locus-specific identifier breakapart probe set to detect translocations involving the *DDIT3* (previously known as *CHOP*) fusion gene at 12q13 (Abbott Molecular, Inc., Des Plaines, Ill.). In brief, a minimum of 100 cell nuclei are required, but in most cases 200 nuclei were counted. Normal cells lacking t(12q13) rearrangement in the *DDIT3* region show 2 fused red and green signals reflecting the 2 intact copies of the *DDIT3* gene, whereas cell nuclei harboring t(12q13) display only 1 fused signal, and a separate green and red signal indicating a translocation. A positive result is interpreted as demonstrating these breakapart signals in more than 2% of nuclei. In addition to *DDIT3*, FISH testing for *MDM2* amplification and for *EWSR1* rearrangement (using a separate breakapart probe kit) was performed in selected cases.

Results

A total of 24 myxoid LPS cases were obtained from 21 patients. An average of almost 4 slides was available for review per case (range: 2-7 slides). One patient had 3 separate FNA biopsies over a 3-year period, and another had 2 separate biopsies 2 years apart. Eleven patients were men (M:F = 1.1:1) with ages ranging from 17 to 76 years (mean: 52 years). Sixteen aspirates (67%) were from the thigh, 3 from the shoulder/arm, and 1 each from the knee, calf, neck, hip, and anterior tibia. Seventeen (71%) were from primary neoplasms, 5 from locally recurrent tumors, and 2 from metastatic deposits. Mass lesions ranged from 2 to 32 cm (mean: 9.7 cm). All cases had histologic confirmation by subsequent surgical resection with 22 diagnosed as myxoid LPS, and 2 as myxoid liposarcoma with high-grade transformation (myxoid/round cell LPS). Concurrent core needle biopsies were not performed at the time of FNA biopsy (Table 1). A specific diagnosis of myxoid LPS was made in 21 out of 24 (87.5%) cases. One case was diagnosed as suspicious for myxoid LPS, and 2 cases (1 primary neoplasm and 1 metastatic) were diagnosed descriptively as spindle cell neoplasm and spindle/round cell neoplasm. Fifteen of 17 (88%) primary neoplasms were diagnosed correctly and specifically as myxoid LPS. Two false positive examples and no false negative cases were encountered (see the following).

The first 7 cases in this series did not have the opportunity for *DDIT3* FISH testing as our molecular laboratory has had this probe for the past 8 years only. The remaining 16 cases since that time except 1 were submitted for FISH analysis. It was unsuccessful in 3 (19%) because of an insufficient number of cells in the CB. Thirteen cases tested within the past 5 years showed a positive result by demonstrating rearrangement of the 12q13 locus. These consisted of *DDIT3* analysis from aspirate smears alone (4 cases), smears plus CB (4 cases), and CB alone (5 cases). There were no false positive or false negative *DDIT3* FISH results. In addition, FISH analysis for *EWSR1* rearrangement (2 cases) and *mdm2* amplification (1 case) were negative. IHC was performed on CB in only 9 cases (Table 1). Its major benefit seemed to be in excluding other neoplasms that were being considered at the time including negative results with *mdm2* or *cdk4* for possible