Original Article

Fine-needle aspiration cytology in soft tissue tumors: How far did we go??

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Abstract

Objective: Assignment of the tumors into various cytological categories and to determine specific sub-typing in individual cases. To correlate the cytological features observed with histological parameters and analyse the reasons for discordant diagnosis.

Materials and Methods: 27 cases, with both cytological and histopathological details, diagnosed as soft tissue tumors (STTs) were included. The lesions were classified into 6 cytological categories.

Results: On fine-needle aspiration cytology (FNAC), 14 cases were reported positive for malignant cells and 13 were reported as benign. On histological follow up discordant lesions were further characterized. Discordance was attributable largely to sampling in lipomatous lesions and interpretation errors due to inattention to clinical history, low volume of these lesions in practice, and overlapping cytomorphologic features with other entities. Sensitivity and specificity was 84.61% and 85.71% respectively and overall diagnostic accuracy was 85.18%.

Conclusion: Soft tissue tumors are rare neoplasms that pose a significant challenge as a result of their morphologic overlap and biological heterogeneity. ‘Time-honored’ histopathology is recognized as the ‘gold standard’ for evaluation of STTs. FNAC can be used as a diagnostic modality in soft tissue lesions due to its lesser cost, ease of performance, safety, along with reasonable specificity and sensitivity. In the current era, where ‘needle is preceding the scalpel’ and the biopsy material is getting limited, our study highlights the role and scope, diagnostic difficulties and pitfalls to be aware of when interpreting these challenging FNACs.

Introduction

Fine-needle aspiration cytology (FNAC) as a diagnostic modality for soft tissue tumors (STTs) is increasingly being used. Their morphologic overlap and biological heterogeneity pose a significant diagnostic challenge. FNAC is popular as a result of its cheap cost, easy performance, safety, along with fair specificity and specificity, both in recurrent cases as well as for the initial diagnosis of STTs especially in terms of sorting out malignant cases.

This study aimed at the assignment of the tumors into various cytological categories and to determine specific sub-typing in individual cases. In this study, we attempted to correlate the cytological features observed with histological parameters. The reasons for discordant diagnosis on histological follow-up were analyzed.

Materials and Methods

We retrospectively retrieved all FNAs of histopathologically diagnosed soft tissue lesions, at the Department of Pathology, during a 2-year period from June 2011 to June 2013. The available clinical information was reviewed along with the histopathological follow-up.

Aspirates inadequate for opinion and when not followed by excision were excluded from the present study.

FNAs were performed using a 22-24 gauge needle. To obtain adequate material, 3-5 passes were used. Smears stained using Papanicolaou, Hematoxylin and Eosin (H and E), and Giemsa were evaluated and interpreted in conjunction with clinical details to render a final diagnosis.

Based on the cytomorphological features, lesions were classified into 6 categories namely spindle cell, lipomatous,
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myxoid, inflammatory, round cell, and pleomorphic type. In cases with mixed components, the specific subtype was assigned to the predominant morphological pattern.

The excised tissue specimens of all the cases were processed routinely, stained with H and E and studied.

The cases with a discrepancy between the cytologic and histologic diagnosis were reviewed to determine the reason. The sensitivity, specificity, positive predictive value, and negative predictive value were calculated considering the false positive and false negative cases for malignant lesions diagnosed on cytology.

Results

Of the 27 cases, a male predominance was noted. Most cases were in age group of 30-50 years, with an average age of 42.11, there were 15 males and 12 females and the extremities were the most common site of involvement. Most of the cases were referred for a primary diagnosis, and only 2 of the evaluated cases were recurrent lesions. On FNAC, 14 cases were interpreted positive for malignant cells whereas 13 were reported as benign conditions or negative for malignant cells [Tables 1 and 2].

The specificity and sensitivity were calculated for malignancy which was 84.61% and 85.71% respectively. The positive predictive value was found to be 84.61% and negative predictive value 84.61%. The overall diagnostic accuracy was 85.18%.

Among the 13 spindle cell tumors, on cytology, 6 were categorized as benign and 7 malignant. Specific diagnoses rendered were nerve sheath tumors (4 cases), synovial sarcoma (2 cases), fibrous histiocytoma (3 cases), fibrosarcoma (2 cases), high grade spindle cell sarcoma (2 cases). Two cases of false negative and one case of false positive were in this category.

Histology was cordant in only one of the 4 lesions in the adipocytic category. The other three, were reported as elastofibroma, fibrous hamartoma of infancy (FHI) and pleomorphic lipoma on histological follow-up, but all had significant adipocyte component.

On cytology, in the myxoid category, 1 benign case was reported as myxoma and 2 cases as myxoid liposarcoma (Figure 1c) and one case as myxofibrosarcoma (Figure 1d). One myxoid liposarcoma was diagnosed as myoepithelioma on histopathology.

In the inflammatory category, one case reported as the granulomatous lesion was a nerve sheath tumor on histopathology. Kimura’s and inflammatory pseudotumor (IPT) were the two cases correctly diagnosed.

In the pleomorphic group, both the cases were labeled as sarcoma. The only case in round cell category incorrectly subtyped as Ewing’s on cytology was a rhabdomyosarcoma (RMS) on histology.

In 5 cases, the behavior was accurately categorized as benign or malignant but were wrongly subtyped. Upon review of these, errors were due to sampling in two benign cases and due to interpretation in two benign and one malignant case.

The discrepancy between the cytological and histopathological diagnosis was noted in 9 cases [Table 3].

The discrepancy between the cytological and histopathological diagnosis was noted in 9 cases [Table 3]. Upon review, there were 2 false-negative cases, dermatofibroma reported as low grade fibromyxosarcoma (LGFMS) and neurofibroma as synovial sarcoma and 2 false positive cases, high grade spindle cell sarcoma reported as ischemic fasciitis [Figure 2c] and myxoid liposarcoma as myoepithelioma [Figure 2d].

In 4 cases, error in interpretation was due to their rarity and lack of familiarity with cytological features whereas in 2 cases, they

Table 1: Benign tumors: Correlation of cyto and histopathological diagnosis

| Cytological category | Total cases | Accurately diagnosed | Benign but not categorized | Benign on FNAC but malignant on histopathology |
|----------------------|-------------|----------------------|---------------------------|---------------------------------------------|
| Spindle              | 6           | 4                    | 0                         | 2                                           |
| Myxoid               | 1           | 1                    | 0                         | 0                                           |
| Inflammatory         | 2           | 1                    | 1                         | 0                                           |
| Lipomatous           | 4           | 1                    | 3                         | 0                                           |

FNAC: Fine-needle aspiration cytology

Table 2: Malignant tumors: Correlation of cyto and histopathological diagnosis

| Cytological category | Total cases | Accurately diagnosed | Malignant but not categorized | Malignant on FNAC but benign on histopathology |
|----------------------|-------------|----------------------|-----------------------------|-----------------------------------------------|
| Spindle              | 7           | 6                    | 0                           | 1                                             |
| Myxoid               | 3           | 2                    | 0                           | 1                                             |
| Inflammatory         | 1           | 1                    | 0                           | 0                                             |
| Pleomorphic          | 2           | 2                    | 0                           | 0                                             |
| Round cell           | 1           | 0                    | 1                           | 0                                             |

FNAC: Fine-needle aspiration cytology

Figure 1: (a) Braid-like elastic fibers in elastofibroma (Giemsa, ×400). (b) Mixture of adipose tissue and cluster of bland spindle cells in a myxoid background in fibrous hamartoma of infancy (Papanicolaou [PAP], ×100). (c) Discrete myxoid stromal fragments with univacuolated lipoblasts and curvilinear vessels in myxoid liposarcoma (Giemsa, ×100). (d) Cellular smears with marked pleomorphism in myxofibrosarcoma (PAP, ×400)
were wrongly called, due to the overlap in the cytomorphological features. In three cases, with benign cytological diagnosis inadequate sampling was the reason for discordance.

Discussion

The diagnosis of soft tissue lesions can be obtained by FNA, core biopsy or open biopsy, each have their own advantages and disadvantages. There have been a number of studies describing the success and limitations of FNAC of STTs. Our study was carried out to highlight aspects of cytological diagnosis of STTs.

In many medical centers, increasingly, FNAC is being used as a diagnostic modality for initial diagnoses, as well as for recurrences and metastases of STTs, thus facilitating clinical decision-making. When compared with open biopsy, this procedure is well-tolerated by patients and risk of complications is minimal, in addition, the multiple passes of the needle make it possible to sample different parts of a tumor, opposed to a single small core biopsy or open biopsy.\[2\]

An almost equal incidence of benign and malignant cases in our series was in contrasting to Rekhi et al., where sarcomas formed a greater proportion of referral cases at their center.\[2\]

In terms of diagnostic efficacy, in malignant cases, we had a sensitivity of 84.61% and specificity of 85.71%. While the specificity was comparable, the sensitivity was much lower to Rekhi et al., which had values of 100% and 87%, respectively.\[2\] But Wakely et al. reported 100% sensitivity and 97% specificity in STT diagnosis with FNAC.\[3\] In our study, 2 (7.4%) cases were FP and 2 (7.4%) cases were FN. Our results showed higher FP values when compared to<1-5% reported in the literature however the FN was found to be within the documented range of 2-15%.\[2\] A study by Nagira et al. had higher figures for false positivity and false negativity.\[4\]

Sampling errors can be attributed to low cellularity, inadequate sampling of the target and copious cystic/bloody/necrotic material.\[1\] Obtaining adequate specimens from deeply seated lesions is a technical pitfall and misdiagnosis of cells from reactive zones around the tumor, correct evaluation of spindle cell lesions, rare soft tissue neoplasms, and “new entities” lacking reproducible cytological criteria are other important challenges.\[5\] Complex heterogeneity of STTs is known to be a limiting factor in their exact categorization.\[5\] Our experience in discordant cases substantiates these observations.

For a successful cytological evaluation, the application of strict reproducible morphological criteria in the context of the clinical findings as well as ancillary techniques is required.\[5\] Liu et al. found that clinical history improved the diagnostic accuracy in bone and soft tissue lesions "for all observers regardless of experience."\[5\]

Our series focused upon the value of cytomorphological subtyping into the six categories. Lesions categorized as malignant belonged to myxoid, spindle cell, round cell, and pleomorphic category in our study. A cytological approach for making a STT diagnosis begins with the familiarity with normal structures, attention to myxoid or metachromatic stromal fragments and a variety of discohesive cells like spindly, round, pleomorphic, polygonal that are indicators of a STT, on aspirates. Cytological categorization with benignancy or malignancy of the subtypes was statistically significant when these features were integrated with clinicoradiological findings.\[3\]

In terms of exact subtyping, which was offered in 18 cases, 76% and 75% of the spindle and myxoid tumors and all pleomorphic tumors, respectively, were suitably categorized. The least concordance was seen in lipomatous tumors (25%). This was in contrast to that of Rekhi et al. who reported maximum congruence in lipomatous and pleomorphic cell category and minimum in spindle cell tumors.\[2\] In the experience of Singh et al., spindle cell lesions were the most diagnostically challenging because of the difficulties in accurately separating benign lesions from low-grade sarcomas and accurately subclassifying the sarcoma.\[2\]
In the lipomatous category, all 4 cases were categorized as benign, but the exact diagnosis was offered in only one case. Pleomorphic lipoma was diagnosed only as lipoma, because of inadequate sampling of characteristic "floret-like" giant cells. A superficial location i.e., neck, in an elderly male, was a helpful clue in excluding a liposarcoma.

In the false positive case of ischemic fasciitis, the reactive stromal cells with nuclear atypia were misinterpreted as malignant cells. Ischemic fasciitis is described as a distinctive fibroblastic proliferation occurring predominantly in elderly, bed-ridden individuals, which can be mistaken clinically, cytopathologically, and histologically for sarcoma.\(^\text{[8]}\) The cytologic findings in this case, when combined with the history of immobilization following ulnar fracture, should have avoided the misdiagnosis of malignancy in a benign, proliferative lesion.

Two of six false-positive cases were proven to be fibromatosis though cytodiagnosis was low-grade spindle cell sarcoma. High cellular yield, pleomorphism, and mitosis in the aspirates from fibromatosis lead to this mistake. Myxoid background, presence of inflammatory cells and binucleate or trirucleate ganglion cells, pale wispy cytoplasm of spindle cells with homogeneous chromatin pattern should be appreciated for a correct diagnosis. Clinical features are also helpful in diagnosis. But immunocytochemistry has got little role.\(^\text{[9]}\)

In the other case of false positive diagnosis, the presence of plasmacytoid round cells in a diffuse myxoid background was mistaken for myxoid liposarcoma. Superficial location and absence of characteristic vasculature were ignored. The myxoid stroma in liposarcomas is typically distributed as discrete stromal fragments rather than as a diffuse film of myxoid material.\(^\text{[7]}\) Cytologic findings of soft tissue myoepithelioma have been not reported in the literature, except for a case report of imprint cytology.\(^\text{[10]}\)

False negative cytology diagnoses could be attributed to interpretation errors, one due to the rarity and other due to overlap in cytological features. LGFMS reported as dermatofibroma is a rare tumor recently being recognized and seldom diagnosed on FNAC. The cytologic features are not specific enough for a definitive diagnosis based on FNAC alone; however, correlating the cytologic and clinical findings can narrow the range of diagnosis.\(^\text{[11]}\) One case of synovial sarcoma was reported as neurofibroma due to its para-splinal location and cytological overlap with limited sampling on USG was the cause for interpretation error.

Sampling error was noted in three of our cases. One case was accurately subtyped as adipocytic but not accurately as pleomorphic lipoma, and the other case was of a nerve sheath tumor which was misinterpreted as a granulomatous lesion, because of superficial ulceration. In spindle cell category, a paraspinal neurofibroma was suggested but was a synovial sarcoma on histopathology. From a practical standpoint, it may not be possible to accurately separate low-grade spindle cell and myxoid sarcomas from benign neoplasms based on cytomorphology alone. FNAC in this instance, still allows the rapid separation of patients who will require tissue biopsy for a definitive diagnosis, thereby obviating multiple clinic visits, eliminating unnecessary procedures, and reducing the overall costs.\(^\text{[12]}\)

The problem of inadequate sampling can be avoided by the use of more stringent adequacy criteria. At present with no established adequacy criteria for soft tissue cytology, the number of inadequate cases varies by a pathologist, institution and study. Finding a threshold whereby sensitivity is maximized, and inadequacy rates are minimized is hard to define.\(^\text{[13]}\)

It has been seen that benign lesions are more difficult to subclassify than malignant lesions. 10 (71%) were subclassified as sarcoma while in contrast, only 7 (53%) could be subclassified as a specific benign lesion. These findings were similar to that of Khabbou et al., who reported subclassification in 83% and 37% of malignant and benign cases.\(^\text{[1]}\)

Most of the smears, in a study of 5 cases of elastofibroma, were paucicellular, and the cellular component consisted of individual cells or clusters of spindled fibroblasts with bland nuclear features and rare mature adipocytes. The acellular matrix composed of elongated rod-like structures with serrated borders or braid-like or fern-like fibers and petaloid globules were the diagnostic component. These characteristic cytomorphologic features are not to be mistaken with any other lesions.\(^\text{[12]}\) Our case of elastofibroma was reported as lipoma. A careful review of occupational history i.e., patient was an elderly manual laborer, bilateral inter-scapular location would have helped in the diagnosis. The paucicellular nature of the lesion was inadvertently mistaken, and the acellular matrix was overlooked in our case.

Cytology literature has few reports of FHI, a rare, benign lesion. The mixture of adipose tissue, a cluster of bland spindle cells in a myxoid and collagenous background is helpful to differentiate this from other infantile soft tissue lesions on cytology. This diagnosis can be made in the proper clinical setting i.e., clinical history, radiological findings, and location of the lesion with awareness of the cytologic features.\(^\text{[13,14]}\) Interpretation error in our case could be a lack of experience and overemphasis on the adipose tissue fragments as the lesion was situated in the breast.

In the inflammatory category, FNAC of a retroauricular mass in a female patient, showed dissociated and clustered lymphocytes, eosinophils, and polykaryocytes. A diagnosis of Kimura’s disease was suggested and was confirmed on histopathology. History, location, and lesional hyperpigmentation with cytological features were recognized to render the diagnosis even in a female patient. It is often diagnosed in male patients.\(^\text{[15]}\)

Although, IPT is placed within the neoplastic category, it is best-regarded as a morphologic entity showing mainly inflammatory cells with a pleomorphic spindle cell component mimicking a tumor. The term, "pseudotumor" is appropriate, and as the atypical spindle cells are myofibroblastic, it can be termed as an inflammatory myofibroblastic tumor. Aspirates usually have an inflammatory background with a predominance of acute or chronic inflammatory cells in different cases. These aspirates are usually suspected to be malignant due to the presence of pleomorphic spindle cells.\(^\text{[16]}\) The case of IPT in
our study was a long standing, discharging lesion in the parotid region. The cytological features were reported, and emphasis for excision was communicated.

In the round cell category, presence of tigroid background and multinucleate and binucleate cells could have prompted a diagnosis of RMS. Periodic Acid Schiff positivity of cells favored a diagnosis of Ewing’s sarcoma. Although cytoplasmic glycogen is characteristic for Ewings, it is neither a specific or constant finding; it can be seen in RMS, lymphoma, and neuroblastoma.[17] In alveolar RMSs, most tumor cells are small and lymphocyte-like, having finely granular chromatin. The finding of cells with more abundant cytoplasm, eccentrically located nuclei, and bi/multinucleated tumor cells in a background of mucousubstance helps in the differential diagnosis.[16]

The relative infrequency of STTs produces unfamiliarity with their histological and cytomorphological features, an increased risk of sampling error due to their tissue heterogeneity and reluctance in soft tissue pathology experts to endorse this technique, which is understandable, if a pathologist has limited exposure and experience to this type of cytologic sample.[10]

In the current study, we have presented clinical, cytological, and histopathological findings of benign and malignant STTs. The specific typing was difficult in the benign category and was fairly accurate in malignant lesions. The reasons for cytohistological discordance were analyzed. This study helped to document cytological findings in rare cases, which would not have been possible if they were excised.

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