Role of Fine Needle Aspiration Cytology in Diagnosis of Soft Tissue Tumors

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Abstract: Fine needle aspiration cytology has many advantages that make it a first-choice diagnostic approach in many tumors. However, its role in diagnosing soft tissue tumors has been debated and at times discouraged. The aim of the study is to review the role of fine needle aspiration cytology in diagnosing soft tissue tumors and to establish cytological criteria for the most encountered soft tissue tumors. The databases were searched up to 2010 and a comprehensive review of the relevant literature was performed, focusing on the followings: utility and limitations of fine needle aspiration cytology in the diagnosis of soft tissue tumors, diagnostic efficacy of fine needle aspiration cytology in the diagnosis of soft tissue tumors, the cytological features of the most commonly encountered soft tissue tumors, the role of fine needle aspiration cytology in differentiating benign soft tissue tumors from soft tissue sarcomas and its role in grading and exact subtyping of soft tissue sarcomas. The findings of this review showed that fine needle aspiration cytology in conjunction with ancillary studies, especially immunohistochemistry, along with the clinical and/or radiographic data can approach a diagnostic accuracy of 95% for the diagnosis of soft tissue tumors. Also, placing the sarcoma into one of the five cytomorphological group (pleomorphic, spindle, myxoid, small round/ovoid and epithelioid) is useful to reach a confident diagnosis of benignity or malignancy and to suggest a type-specific diagnosis. However, subtyping or grading spindle cell sarcomas as well as lipomatous tumors are often challenging and the use of immunohistochemistry is mandatory for proper diagnosis of these tumors.
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1. Introduction

Soft tissue tumors (STTs) have been considered to pose some of the greatest diagnostic challenges in surgical pathology. According to the latest World Health Organization (WHO) classification, more than 100 benign subtypes, over 50 variants of sarcoma and a number of 'border-line' entities have been described for STTs (Fletcher, 2006). According to Egyptian mortality statistics 2004, death due to soft tissue sarcoma (STS) represents 2.74% of all cancer deaths (Elattar, 2006). Fine needle aspiration cytology (FNAC) has many advantages that make it a first-choice diagnostic approach in many tumors as it is an outpatient procedure, it doesn't need anesthesia and it permits sampling of different parts of a large tumor to evaluate its heterogeneity (Domanski et al., 2005).

However, the cytological diagnosis of STTs, based on FNAC, has been debated and at times discouraged (Weiss and Goldblum, 2008). Obtaining sufficient specimens from deeply seated small and necrotic/cystic lesions is technically a potential pitfall. Sometimes only necrotic tissue is obtained. Some benign lesions can contain atypical cells such as nodular fasciitis and some malignant tumors such as synovial sarcoma (SS) or well-differentiated liposarcoma (LPS) have rather bland cytology (Maitra et al., 2000). On the other hand, Bharat et al. (2007) evaluated 127 cases of FNAC smears from STTs, diagnosed over a period of 5 years and stated that FNAC is fairly specific and sensitive in STTs diagnosis for primary, recurrent and metastatic lesions and that some cytological types, especially round cell and pleomorphic sarcomas, can be quickly identified. In another study carried out by Kitagawa et al. (2003) to evaluate the usefulness of FNAC for the preoperative diagnosis of STTs of the hand, they concluded that FNAC is a useful diagnostic tool, especially in its ability to distinguish between malignant and benign lesions of the hand, but its main limitation in diagnosing hand tumors, is the difficulty in diagnosing schwannoma and fibrous tumors, which are common. In addition, Khalbuss et al. (2010) proved that there can be a high sensitivity and specificity in diagnosing bone and soft tissue lesions by FNAC.

So, it is apparent that there has been and stills a debate on the usefulness of FNAC in diagnosing STTs. Also the accurate cytological features for classifying and diagnosing STTs haven't yet been settled. Therefore, this study was carried out to give an overview about STTs classification, their grading and staging. Also, the role of FNAC in diagnosing STTs will be reviewed and the cytological features for classifying and diagnosing STTs as a guide for early accurate diagnosis will be studied.

2. Materials and Methods

The Databases were searched up to 2010. A comprehensive review of the relevant literature was performed, focusing on the followings: utility and limitations of FNAC in the diagnosis of STTs, diagnostic efficacy of FNAC in the diagnosis of STTs, the cytological features of the most commonly encountered STTs, role of FNAC in differentiating benign STTs from STS and role of FNAC in grading and exact subtyping of STS.

The following methodological items were taken into account: (1) type of study, (2) sample size, (3) sample selection, (4) laboratory techniques and (5) statistical analysis.

3. Review of Literature

3.1 Definition and Classification

STTs are defined as mesenchymal proliferations that occur in the extraskeletal, nonepithelial tissues of the body, excluding the viscera, coverings of the brain and lymphoreticular system (Kumar et al., 2007). The most recent classifications of STTs have been based principally on the line of differentiation of the tumor, that is, the type of tissue formed by the tumor rather than the type of tissue from which the tumor arose (Wiess and Goldbulm, 2008). The most significant conceptual changes in the last WHO classification of STTs, is that it revised categorization of biological behavior, allowing for two distinct types of intermediate malignancy, identified respectively as 'locally aggressive' and 'rarely metastasizing' in addition to 'benign' and 'malignant' types (Fletcher et al., 2002). Also it acknowledged the poorly defined nature of the categories known as malignant fibrous histiocytoma (MFH) (which in reality represents undifferentiated pleomorphic sarcoma) and haemangiopericytoma (HP) (most examples of which are closely related to solitary fibrous tumor (SFT). It also categorized the so-called angiomatoid MFH and extraskeletal myxoid chondrosarcoma (EMC) into tumors of uncertain differentiation (Fletcher, 2006).

Most benign STTs do not recur locally while locally aggressive STTs often recur locally and are associated with a local infiltrative growth pattern. On the other hand, rarely metastasizing STTs are often locally aggressive but show the well-documented ability to give rise to distant metastases in occasional cases. Malignant STTs (known as STS) are characterized by local destructive growth and a significant risk of distant metastasis, ranging in most instances from 20% to 100%, depending upon histological type and grade (Weiss and Goldblum, 2008).

3.2 Frequency of STTs in Egypt

In Egypt, according to the National Cancer Institute (NCI) records registry, the number of the newly diagnosed STTs cases from the year 2002, 2003 and 2005 constitute 2.74% of total malignancies recorded with a male predominance of 60.07% and with a high percentage of pediatrics, 28%. They were thus ranked the third amongst pediatric tumors, after lympho-hematopoietic and bone tumors (Elattar, 2006). Table (1) shows the relative frequency of the different types of STS.

Table (1): Relative frequency of the histopathological types of STS in Egypt (Elattar, 2006).

Type	%
LPS	16.04
Rhabdomyosarcoma (RMS)	13.80
Primitive Neuroectodermal Tumor (PNET)	13.06
MFH	10.07
Synovial sarcoma (SS)	9.70
MPNST	7.09
Fibrosarcoma	4.48
Leiomyosarcoma (LMS)	3.36
Alveolar soft part sarcoma (ASPS)	1.87
Vascular sarcomas	1.87

3.3 Histological grading of STS

Grading, based on histological parameters only, evaluates the degree of malignancy and mainly the probability of distant metastasis (Conidre et al., 2001). The two most widely used grading systems for STS are those of the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC), also known as the French Federation of Cancer Centers sarcoma group and the United States National Cancer Institute (NCI) (Fletcher, 2006).

3.4 Staging of STS

The tumor size, Regional lymph node involvement, Distant metastasis staging system (TNM) used for STS was developed by the International Union against Cancer (UICC) and the American Joint Committee on Cancer (AJCC). This system incorporates histological grade as well as tumor size and depth, regional lymph node involvement and distant metastasis (Greene et al., 2002).

3.5 Diagnosis of STTs by FNAC

Diagnosis, as well as prognosis of STTs has been based on the assumption that pathologists would have significant amounts of tissue on which to render a diagnosis and grade. Although incisional biopsy is the golden standard for the diagnosis of deep soft tissue masses, reliance on minimally invasive techniques as FNAC to procure diagnostic tissue has become more common (Weiss and Deyrub, 2006). Other diagnostic methods include IHC, Electron Microsopce (EM), DNA analysis and molecular diagnostics.

FNAC has many advantages that make it a first-choice diagnostic approach in many tumors. It is an

outpatient procedure, it doesn't need anesthesia and it permits sampling of different parts of a large tumor to evaluate its heterogeneity (Domanski et al., 2005). Also, properly performed, FNAC is the least tissue-invasive diagnostic procedure and the risk for sarcoma-cell spread is negligible (Akerman, 1998). In the hands of experienced cytopathologists, FNAC in conjunction with ancillary techniques has a diagnostic accuracy approaching 95% for the diagnosis of soft tissue malignancy **(**Kocjan, 2004). Additionally, as therapy and prognosis are heavily dependent on the grade and stage of the tumor, Singh et al. (2007) stated that most of STS can be successfully subtyped and even graded by FNAC.

On performing FNAC to STTs, five passes at most should be made with the needle being moved back and forth through the specimen without exiting the skin surface**.** It's recommended to sample tissue from at least three different parts from the tumor to assess its heterogeneity (Wakely and Kneisl, 2000). The microscopic evaluation of STTs obtained by FNAC should be based on both wet fixed Hematoxylin and Eosin stain (H&E) or Papanicolaou stain (Pap) and air-dried May Griinwald- Giemsa (MGG) or Diff-Quik smears. The wet-fixed material is superior for evaluation of nuclear detail such a chromatin structure and nucleoli while the MGG staining gives excellent information on cytoplasmic detail and the background matrix (Weiss and Deyrup, 2006).

There are, however, certain limitations for the use of FNAC in the diagnosis of STTs. The main pitfall is that the needle may miss the tumor and a false diagnosis is made on the basis of cells aspirated from the tissue surrounding the tumor (Singh et al., 2007). Insufficient material obtained by FNAC may result in a false diagnosis or preclude any diagnosis at all (Fletcher et al., 2002). In addition, there are some rare STTs, in which the cytological criteria that allow their correct diagnosis as benign or malignant, as well as to type them, have not been established. Comparative histological-cytological studies of reasonably large series of these tumors are often lacking (Fuju, 2006). Examples of these tumors are lipoblastoma, chondroid lipoma, perineurioma, aggressive angiomyxoma, SFT of soft tissue, mixed tumor of soft tissue, parachordoma and spindle cell LPS (Singh et al., 2004). Another important pitfall in depending on FNAC in the diagnosis of STTs is misinterpretation of the cellular material. This mostly occurs in the diagnosis of benign lipoma variants as pleomorphic lipoma, hibernoma or lipoblastoma and in the interpretation of soft tissue metastases from pleomorphic carcinoma or melanoma as pleomorphic sarcoma. Also, metastases from renal clear cell carcinoma might be misinterpreted as pure round cell LPS (Brooks, 1996).

The benefits and limitations of FNAC in the definitive diagnosis of a STS must be weighed in relation to the proposed treatment (Akerman, 1998). The main purpose of FNAC in soft tissue lesions is to inform the surgeon whether the tumor in question is a true soft tissue lesion/tumor or a STS or a soft tissue metastasis (Kilpatrick et al., 2001). In case of sarcoma, the standard treatment in the majority of cases is primary radical surgery (a minimum of 1 cm to 2 cm margins of normal tissue), sometimes followed by radiotherapy. The type of surgical intervention depends more on the site (subcutaneous or deep), size and the relation of the sarcoma to vessel, nerve bundle and periosteum than on the histotype. Thus a reliable diagnosis of sarcoma is sufficient for the surgeon in those cases where primary radical surgery is the proposed treatment (Liu et al., 1999). When the treatment includes neoadjuvant therapy (radiotherapy or chemotherapy) followed by surgery, the FNAC diagnosis must equal that of a histopathological evaluation as regard histotype and malignancy grade (Kilpatrick et al., 2001). At present, neoadjuvant therapy is used for some cases of STS as RMS, neuroblastoma and extraskeletal Ewing's sarcoma/primitive neuroectodermal tumor (ES/PNET) family of tumors (Weiss and Goldblum, 2008).

For FNAC specimens, several studies recommend a classification approach that divides STTs into **five** major cytomorphologic subgroups based on the predominant cytological appearance of the specimen on aspiration smears: pleomorphic, spindle cell, myxoid rich, small round/ovoid cell and epithelioid. In most cases, once a cytomorphological subtype has been determined, the corresponding histological grade in many cases is definitional (Singh et al., 2004). Such classification has been used in many comparative cytological-histological studies to evaluate the role of FNAC in the diagnosis of STTs (Costa et al., 1996; Kilpatric et al., 2001; Mathur et al., 2003*;* Dey et al., 2004 and Bahrat et al., 2007). The most reported pitfall in this classification is that it is not possible to classify all STTs into these five groups. In addition, overlapping cytological features can occur. For example, RMS can display a variety of cytomorphological features, ranging from a small round cell to spindle cell morphology as well as the presence of a myxoid background in the botryoid forms. Likewise, SS may demonstrate a predominant epithelioid cell pattern rather than the classic spindle cell pattern (Singh et al., 2004). However, such a categorization may be useful to reach a confident diagnosis of benignity or malignancy, to suggest a type-specific diagnosis as well as in the recognition of important differential diagnoses (Akerman and Domaniski, 2003).

In the following sections, the diagnostic features of each of the above mentioned patterns will be discussed as well as the most common types of STTs belonging to

each of them and the limitations of the diagnosis of each.

3.5.1 Pleomorphic cell pattern

The typical features are a marked variation in cellular and nuclear size and shape and in case of sarcoma marked nuclear pleomorphism including atypical multinucleated tumor cells and prominent nucleoli (Akerman et al., 1980). Benign STTs in this category are nodular fasciitis and pleomorphic lipoma. Typical examples of sarcomas are undifferentiated pleomorphic sarcoma (pleomorphic sarcoma of the MFH type), pleomorphic LMS, pleomorphic LPS and the less common pleomorphic RMS (Singh et al., 2004). In most cases of pleomorphic STS, the cytological features are not diagnostic for subtyping beyond a diagnosis of "pleomorphic sarcomas, not otherwise specified" (Singh et al., 2004). Wrong (2008) have reported that, adult patients with pleomorphic sarcomas, regardless of the histological subtype, are treated similarly with complete surgical excision and radiation therapy and/or chemotherapy. This is due to the fact that prognosis and treatment responses are approximately the same across the group. The most common differential diagnostic problems arise in the separation of pleomorphic sarcomas from sarcomatoid carcinomas from various sites (lung, kidney, pancreas, and thyroid), malignant melanoma, and anaplastic lymphoma. All of these entities can present with highly cellular smears with a predominance of dyscohesive cells that are markedly pleomorphic and sometimes multinucleated. Careful review of the clinical history along with ancillary studies (panel of IHC stains) is crucial for accurate classification (Singh et al., 2007).

The following table shows the most common STTs with pleomorphic pattern and their diagnostic morphological features:

3.5.2 Spindle cell pattern

The spindle cell pattern is characterized by predominance of more or less atypical spindle cells with fusiform or ovoid nuclei and elongated uni- or bipolar cytoplasm. The cells are mostly arranged in sheets or fascicles, but dissociated cells are often present. A small population of larger rounded, polygonal or triangular cells with relatively abundant cytoplasm and nuclei of variable size and shape may be present in some sarcomas (Akerman and Domaniski 2003).

Common examples of benign tumors are neurilemoma, spindle cell lipoma, desmoid fibromatosis, SFT, HP and deep leiomyoma. Typical spindle cell sarcomas include the LMS, MPNST, monophasic SS, dermatofibrosarcoma protuberans (DFSP), spindle cell gastrointestinal stromal tumor (GIST), fibrosarcoma and angiosarcoma (Singh et al., 2004**).**

Table (2): The most common soft tissue tumors with pleomorphic pattern and their diagnostic morphological features (Dahl et al., 1981; Akerman and Rydholm 1983; Walaas et al., 1986; Akhtar et al., 1992; Almeida et al., 1994; Liu et al., 1999; Thirumala et al., 2000; Clayton et al., 2001; Kong and Cha 2004; and Khalbuss et al., 2010).

Tumor	Diagnostic Morphological features
Nodular fasciitis	- Abundant myxoid background. - Pleomorphic population of myofibroblasts: spindly, rounded or triangular, with cytoplasmic processes and admixture of inflammatory cells.
Pleomorphic Lipoma	- Fragments of mature fat. - A variable number of large cells with hyperchromatic nuclei and eosinophilic cytoplasm - 'Floret cells' are seen.
Undifferentiated pleomorphic sarcoma (MFH-type sarcoma)	- Cellular smears with necrosis. - Variable proportions of atypical and pleomorphic spindle cells, polygonal cells and multinucleated large cells.
Pleomorphic LMS	- Cellular smears with necrosis. - Tumor cells have marked cellular and nuclear pleomorphism with abundant eosinophilic cytoplasm. - Multinucleated tumor cells.
Pleomorphic LPS	- Presence of highly atypical multinucleated lipoblasts
Pleomorphic RMS	- Atypical rhabdomyoblasts with abundant eosinophilic cytoplasm

The group of spindle cell sarcomas is the most diagnostic challenging because of difficulties in accurately separating benign lesions from low-grade sarcomas and accurately subclassifying the sarcoma (Singh et al., 2007). Also, Domaniski et al. (2006) have shown that the two major criteria used to designate a FNAC specimen as a sarcoma, namely, moderate to high smear cellularity and hyperchromatic nuclei in almost all sampled cells; do not always allow accurate separation and/or grading among the spindle cell sarcoma group. Benign mesenchymal lesions often demonstrate marked dyscohesiveness and hypercellularity that, in some cases, result in destructive changes clinically and radiographically mimic a sarcoma (Li et al., 2001). Because metastases outnumber primary STS, nonsarcomatous malignancies must be included in the differential diagnosis of spindle cell sarcomas. Sarcomatoid carcinomas, mesotheliomas, malignant melanomas, and non-Hodgkin lymphomas associated with sclerosis present the most difficulty in accurate separation from primary spindle cell sarcomas. Correlation with the past medical history and IHC stains is crucial in rendering an accurate diagnosis (Singh et al., 2004).

The following table shows the most common STTs with spindle cell pattern and their diagnostic morphological features:

Table (3): The most common soft tissue tumors with spindle cell pattern and their diagnostic morphological features by H&E stain (Dahl et al., 1981; Akerman and Rydholm 1983; Ryd et al., 1986; Lopez et al., 1990; Kilpatrick et al., 1996; Boucher et al., 2000; Clayton et al., 2001; Sawh et al., 2001; Li et al., 2001; Domanski and Gustafson 2002; Akerman and Domaniski 2003; Singh et al., 2004; Wrong, 2008; Domaniski et al., 2006; Akerman and Domanski 2007; Owens et al., 2007 and Kaur et al. 2010).

Tumor	Diagnostic Morphological features
Neurilemoma (Schwannoma)	- Fragments with fibrillary background and spindle-shaped cells forming Antoni A, while others have loose appearance with cells having slender cytoplasmic processes (Antoni B)
Spindle cell lipoma	- A mixture of mature adipose tissue and dispersed or clustered, bland-looking spindle cells, in a myxoid background
Desmoid Fibromatosis	- Fragments of paucicellular collagenous stroma. - Fibroblasts with spindle-shaped nuclei are seen.
SFT	- Dispersed bland cells mixed with cell-tight three-dimensional fascicle-like clusters. - Nuclei with bland chromatin and
Deep leiomyoma	- Clusters of dispersed cells and small aggregates of cells with elongated, blunt-ended, or cigar-shaped nuclei.
LMS	- Cells have moderately pleomorphic elongated blunt-ended nuclei, with prominent nucleoli and intranuclear inclusions.
MPNST	- A fibrillary background. - Spindle-shaped cells with elongated, wavy nuclei. - Presence of pleomorphic and/or multinucleated tumor cells
Monophasic SS	- Dispersed spindle shaped cells and branching fragments of tightly packed cells - Cells have ovoid bland nuclei and inconspicuous nucleoli
DFSP	-Tumor cells are uniform spindle cells, either dispersed or clustered in three-dimensional cell-rich fascicles (fascicular arrangement). - Stripped nuclei are often seen.
Spindle cell GIST	- Cohesive clusters of cells with spindly, ovoid, comma-shaped nuclei and scanty cytoplasm with cytoplasmic processes.
Fibrosarcoma	- Uniform population of dispersed and clustered atypical spindle shaped cells, with fusiform nuclei
HP	-Hypercellular aspirate formed of minimally atypical spindle shaped cells arranged in fragments traversed by vascular channels.
Angiosarcoma	- Hypocellular aspirate with predominantly single spindled to rounded cells with abundant vacuolated cytoplasm and pleomorphic nuclei. - Vasoformative features: intracellular RBCs, well-formed vessels and microacinar formation.

3.5.3 - Myxoid pattern

Although myxoid changes can be seen in a variety of STTs, it's not usually consistently seen as a dominant feature of the tumor (Singh et al., 2004). Aspirates of myxoid tumors often look like droplets of glue. Under low power magnification there is an evident myxoid background matrix, faintly pink in H&E stain and faintly green in Pap stain. The cellular pattern is variable: pleomorphic, spindly or round cells (Akerman and Domanski 2003).

A myxoid pattern is common to several STTs. Examples of benign tumors are intramuscular myxoma, liboplastoma, ossifying fibromyxoid tumor (OFMT), perineurioma, parachordoma and mixed tumor of soft tissue (myoepithelioma). The most common sarcomas are myxofibrosarcoma and myxoid LPS, low-grade fibromyxoid sarcoma and extraskeletal myxoid chondrosarcoma (EMC) (Singh et al., 2004).

The following table shows the most common STTs with myxoid pattern and their diagnostic morphological features:

Table (4): The most common soft tissue tumors with myxoid pattern and their diagnostic morphological features (Akerman and Rydholm, 1983; Housini and Dabbs 1990; Szadowska and Lasota 1993; Verma et al., 1993; Lindberg et al., 1999; Minami et al., 2001; Akerman and Domanski 2003; Hornick and Fletcher, 2003; López-Ferrer et al., 2005; Jakowski and Wakely 2007; Hong et al., 2008; Ran et al., 2008; Colin et al. 2010 and Zardawi 2010).

Tumor	Diagnostic Morphological features
Intramuscular myxoma	- Scattered vessel fragments - Cells have elongated uniform nuclei and cytoplasmic processes
Lipoblastoma	- Fatty tissue fragments. - Branching strands of capillaries - Vacuolated lipoblast-like cells.
OFMT	- Mildly atypical cells which may be dissociated, or arranged in rosette-like structures,
Perineurioma	- Elongated cells with fusiform nuclei and cytoplasmic processes arranged in clusters
Parachordoma	- Cells are polygonal with abundant cytoplasm and bland nuclei. -Some cells have vacuolated cytoplasm and eccentric nuclei.
Mixed tumor of soft tissue	- Cells are spindle-shaped or rounded epithelioid-like grow in rows, clusters or groups
Myxofibrosarcoma	- Fragments of curved vessels - Atypical spindle cells with scattered large polygonal cells - Some cells have a vacuolated cytoplasm or contain droplets of mucoid material (violet in MGG stain)
Low-grade fibromyxoid sarcoma	- Homogenous population of spindle-shaped cells with mildly atypical nuclei - No vessel fragments.
Myxoid LPS	- Tumor tissue fragments with "chicken wire" capillary vessels, and vacuolated lipoblasts
EMC	- Variable arrangement of cells: clusters and branching strands. - Cells are rounded, elongated and fusiform with bland nuclei and vacuolated cytoplasm

3.5.4- Small round/ovoid cell pattern

Round cell sarcomas predominate in the pediatric population, and, in contrast to adult patients, definitive

cell typing is necessary (Singh et al., 2004). Smears are typically cellular and composed of small to medium-sized cells with rounded or ovoid nuclei and a variable amount of cytoplasm. The shape of the cells is variable: rounded, ovoid or triangular. Nuclei are often bland and nucleoli are small (Bahrat et al., 2007). This pattern is shown mainly by glomus tumor, neuroblastoma, extraskeletal ES /PNET, RMS (especially alveolar), desmoplastic small round cell tumor (DSRCT) and small cell variant of SS (Franco et al., 2007).

In rare cases, it may be difficult to correctly classify this group of sarcomas by histological examination. However, correct cell typing is often possible and achievable in 92% of all round cell sarcomas by FNAC with the judicious use of ancillary studies (IHC, EM and cytogenetics) (Liu et al., 1999).

The following table shows the most common STTs with small round/ovoid cell pattern and their diagnostic morphological features:

Table (5): The most common soft tissue tumors with small round/ovoid cell pattern and their diagnostic morphological features (Seidal et al., 1982; Silverman et al., 1988; Bennert K and Abdul-Karim, 1994; Renshaw et al., 1996; Akerman et al., 1996; Kilpatrick et al., 1999; Layfield et al., 1999; Liu et al., 1999; Silverman et al., 2000; Handa et al., 2001; Granja et al., 2005 and Fuju 2006).

Tumor	Diagnostic Morphology features
Glomus tumor	- Myxoid fibrillary background - Cells are of medium size with poorly defined cytoplasmic borders and rounded bland nuclei
Neuroblastoma	- Cells with hyperchromatic nuclei and cytoplasmic processes arranged in rosette-like structures with a central fibrillary core
ES/PNET family; classic ES	- Highly cellular aspirate. - Double cell population: *Large cells with abundant vacuolated cytoplasm and rounded nuclei (Large light cells) *Small cells with irregular dark nuclei and scanty cytoplasm (Small, dark cells).
ES/PNET family; PNET	- Pleomorphic cells with cytoplasmic processes. - Rosette-like structures.
Alveolar RMS	- Cells are small with scanty vacuolated cytoplasm and prominent nucleoli. - Rhabdomyoblasts: tadpole cells with eccentric nuclei and eosinophilic cytoplasm.
DSRCT	- Cells are small with scant vacuolated cytoplasm and rounded nuclei with small nucleoli, showing rosette-like arrangement.
Small cell variant of SS	- Small cells with scanty cytoplasm and bland nuclei admixed with large cells with abundant cytoplasm and prominent nucleoli.

3.5.5- Epithelioid Cell Pattern

The epithelioid cell pattern is created by cells with epithelioid features: rounded or polygonal cells with distinct cytoplasmic borders, abundant cytoplasm, and rounded, ovoid or irregular nuclei. Nucleoli are often prominent. The tumor cells are arranged in groups, tight clusters or are dissociated. Stripped nuclei are a common finding (Akerman and Domaniski 2003).

This pattern is the least frequently encountered group on FNAC specimens. Typical examples of benign tumors are granular cell tumor (GCT), adult rhabdomyoma and paragangliomas. The most common sarcomas are epithelioid sarcoma, clear cell sarcoma, ASPS, malignant extrarenal rhabdoid tumor, epithelioid cell gastrointestinal stromal tumor (GIST) and epithelioid variant of angiosarcoma (Bahrat et al., 2007). The cytomorphological features among this group of sarcomas show considerable overlap necessitating the use of ancillary studies with IHC to make a specific diagnosis and for separation from non-sarcomatous malignancies (Singh et al., 2007).

The following table shows the most common STTs with small epithelioid cell pattern and their diagnostic morphological features:

Table (6): The most common soft tissue tumors with epithelioid cell pattern and their diagnostic morphological features (Mondal 1995; Akhtar et al., 1994; Gupta et al., 1998; Maruyama et al., 1998; Zeppa et al., 1998; Logrono et al., 1999; Domaniski and Dawiskiba 2000, Zaharopoulos 2001; Cardillo et al., 2001; Li et al., 2001; Mallik et al., 2001; Wieczorek et al., 2001; Creager et al., 2002; Kwon et al., 2002; McGregor et al., 2003; Singh et al., 2004; Laforga 2005; Jin and Saleh 2009 and Min et al., 2010).

Tumor	Diagnostic Morphological features
Granular cell tumor	- Individual cells and cells in cohesive clusters are seen.
Adult rhabdomyoma	- Large epithelioid cells with cross striation in the cytoplasm.
Paraganglioma	- Loose clusters of cells separated by bands of connective tissue strands - Cells have pleomorphic spindled or oval nuclei. - Reddish cytoplasmic granules on MGG stain.
Epithelioid sarcoma	- Cells are medium-sized to large with large nucleoli. - Admixture of lymphocytes, plasma cells and histiocytes.
Clear cell sarcoma	- Cells in small clusters showing intranuclear pseudoinclusions and intracytoplasmic melanin
Alveolar soft part sarcoma	- Hemorrhagic aspirate - Alveolar arrangement of tumor cells can be seen.
Malignant extrarenal rhabdoid tumor	- Grey blue paranuclear cytoplasmic globular inclusions are seen in the tumor cells.
Epithelioid cell GIST	- Tumor cells are rounded with abundant cytoplasm and rounded nuclei.
Epithelioid angiosarcoma	- Both dispersed cells and branching tumor tissue fragments of tightly packed epithelial-like cells showing mild to moderate nuclear atypia.

3.6 Diagnostic efficacy of FNAC in the case of STTs

In terms of diagnostic efficacy, Khalbuss et al.

(2010) reported a high overall sensitivity of 96% and specificity of 98% for the FNAC diagnosis of soft tissue and bone lesions, and a very low rate (3%) of inadequacy. Bahrat et al. (2007) concluded that FNAC had 100% sensitivity and 87% specificity in the diagnosis of STTs. These were comparable to the results of Nagira et al. (2002) wherein the respective values were 92% and 97%. In another series, Wakely and Kenisl (2000) reported 100% sensitivity and 97% specificity in STTs diagnosis with FNAC. Layfield et al. (1986) achieved 95% sensitivity and specificity while dealing with these lesions. In Khalbuss et al. (2010) study on 1114 soft tissue and bone FNAC specimens, there were 15 false negative (FN) (malignant tumor diagnosed as benign cytologically) diagnoses that were most commonly due to sampling error and 3 false positive (FP) (benign tumor diagnosed as malignant cytologically) diagnoses, which were attributable to errors in interpretation due to the misinterpretation of reactive stromal cells with therapy-related changes as malignant cells. In Bahrat et al. (2007) study, 2 cases (1.57%) were FP and none was FN. While a study on 517 STTs aspirates by Akerman et al. (1985) revealed a 2.9% FP rate, the subsequent studies by Wakely and Kenisl (2000) and by Kilpatrick et al. (2001) yielded a single case of FN and nil FP. This was in contrast to a study by Nagira et al. (2002) who identified higher figures for false positivity and false negativity. In Khalbuss et al. (2010) and Bahrat et al. (2007) studies, the results were comparable to the documented range of <1%-5% (FP) and 2-15% (FN) (Layfield et al., 1986; Bommer et al., 1997; Kilpatrick et al., 2001 and Nagira et al., 2002). An overall concordance of 98% in Khalbuss et al. (2010) is comparable to results of Bahrat et al. (2007) and Shah et al. (2003). Also, Singh et al. (2004) reported that in the hands of experienced cytopathologists, FNAC in conjunction with ancillary techniques has a diagnostic accuracy approaching 95% for the diagnosis of malignancy. Besides, the presence of a cytopathologist for onsite evaluation and the presence of concurrent core biopsy in selected cases, which allow for optimization of the FNAC in obtaining sufficient material and provide immediate cytological-histological correlation, respectively are additionally important factors in the success of FNAC in diagnosing STTs (Khalbuss et al., 2010).

However, Khalbuss et al. (2010) reported that the more problematic group was the group of inadequate FNAC specimens. Although only one study defined adequacy in soft tissue FNAC biopsies as the presence of at least 5 clusters of 10 unobscured cells on the majority of slides (Palmer et al., 2000), yet there are no established adequacy criteria for bone and soft tissue cytology which results in variation in the number of inadequate cases by pathologist, by institution, and by study. Also, the authors concluded that benign STTs are more difficult to subclassify than malignant lesions. In addition, there are only a few studies documenting how well FNAC can subtype previously undiagnosed STS, and the results vary widely, with an average 50–70% success rate (Akerman and Rydholm, 1983; Trovick et al., 1998; Liu et al., 1999; Kilpatrick et al., 2001; Domaniski et al., 2006 and Domaniski 2007). In a series carried out by Kilpatrick et al. (2001) on 140 patients to evaluate the role of FNAC in the primary diagnosis of STS, they found the accuracy of FNAC for histological subtyping to be greater for pediatric sarcomas (92%) (with the use of ancillary studies) than for adult sarcomas (52%). The authors further showed that if one is able to subtype or at the least, place the sarcoma into the proper cytomorphological group (pleomorphic, spindle, etc.) then a specific grade was not needed for the initiation of treatment because in most cases, the histological grade is readily apparent. In their series, the FNAC diagnosis was sufficient to begin definitive therapy in 83% of patients with STS. Jones et al. (2002) have shown similar results supporting the opinion that FNAC can accurately subtype and grade STS in most cases. In their series of 107 FNAC (77 with corresponding surgical material available), only low-grade sarcomas were undergraded in a significant minority of cases, reducing the utility of FNAC when this group of neoplasms is encountered.

As previously mentioned, many studies recommend dividing STTs into one of five major cytomorphological subtypes based on the predominant morphology: myxoid, spindle cell, round cell, pleomorphic, and polygonal/epithelioid cell. However, it should be recognized that overlapping cytological features can occur; therefore, some tumors might be considered in the differential diagnosis of more than one category. For example, features of SS could be placed in the epithelioid/polygonal, small cell and spindle cell groups (Bennert and Abdul-Karim, 1994 and Kilpatrick et al., 1999). Several studies show also that grading or subtyping of spindle cell sarcomas by FNAC alone is often challenging (Kitagawa et al., 2003; Singh et al., 2004; Bahrat et al., 2007 and Singh et al., 2007). Other studies (Palmer et al., 2000 and Kilpatric et al., 2001) have found similar difficulties when diagnosing lipomatous tumors by FNAC and recommend that deeply seated soft tissue lesions that appear predominantly fatty by current imaging techniques should be evaluated by incisional or excisional biopsy techniques. Also Singh et al. (2004) have concluded in their review of the utility and diagnostic challenges of FNAC in the diagnosis of STS that the epithelioid cell and spindle cell groups are the most challenging to accurately subclassify and grade based solely on cytomorphologic features.

Most authors agree that a definitive cytological

diagnosis must be based on a combination of the cytological findings (ie, adequate specimen, cytomorphology) correlated with results of ancillary studies (IHC, flow cytometry, cytogenetic analysis and EM), along with the clinical and/or radiographic data (Singh et al., 2004). Also, Khalbuss et al. (2010) supported the idea that the majority of malignancies involving soft tissue and bone can be diagnosed and subclassified by FNAC when adequate history, ancillary studies, and onsite evaluation are used. Ancillary diagnostic procedures especially IHC plays an important role in the workup of small round cell, spindle cell, and epithelioid sarcomas (Shah et al., 2003). Table (7) outlines the IHC screening panels for the three categories of tumors for which it is clinically most useful in the rendering of an accurate diagnosis. Also, table (8) shows the most common genetic changes used in the molecular diagnosis of STTs (Miettinen 2006 and Wardelmann et al., 2010).

Table (7): Immunohistochemical screening panels for the round cell, spindle cell and epithelioid cell sarcomas (Singh et al., 2004).

Round cell sarcomas	**Spindle cell sarcomas**	**Epithelioid sarcomas**
***RMS** MyoD1 and Desmin+, CK+/-	***Synovial sarcoma** CK+, EMA+, CD99+, S-100+,Desmin-	***Epithelioid sarcoma** CK+, CD34+, Vimentin+, S-100-, CD30-, CD45-
***ES/PNET** CD99+, CK+/-, S-100-,Desmin-, CD56-	***MPNST** S-100+(weak, focal), CD34 +/-, Desmin-, CK-	***Clear cell sarcoma and metastatic melanoma** S-100+,HMB45+, Melan-A+, CK-
* **DSRCT** CK+, Desmin+, S-100-, CD99+/-	***LMS** Desmin+, Muscle actin+, Vimentin+,	***Alveolar soft part sarcoma** MyoD1 and Myogenin+/-
***Non sarcomatous group:** **-Lymphoma**: CD45+,CD99+/- **-Small cell carcinoma**: CK+, NSE+, Synoptophysin+ - **Melanoma**: S-100+,MB-45+	***DFSP** CD34+, CK-,S-100-, Desmin-,Muscle actin-	***Non sarcomatous group:** **-Ki-1 Lymphoma**: CD30+,CD45+/-, CK-, S-100- **-Carcinoma**: CK+, CD30 and CD34+.

4. Summary and Conclusion

Although FNAC is a widely accepted and established diagnostic technique in diagnosing the presence of primary malignancies, metastatic disease, and benign nonneoplastic lesions, but its role in the evaluation of STTs has remained controversial, especially as the primary modality for establishing an initial diagnosis. Therefore, this study was carried out to review the utility and pitfalls of FNAC in the primary diagnosis of STTs, to highlight diagnostically challenging lesions and comment on the limitations of FNAC in providing a definitive diagnosis.

Table (8): The genetic changes used in the molecular diagnosis of some soft tissue tumors (Miettinen 2006 and and Wardelmann et al., 2010).

Tumor	**Affected genes**
GIST	C-KIT mutations PDGFRA mutations
ES	EWS-FLI1 EWS-ETV1 EWS-ERG
Alveolar RMS	PAX3-FKHD PAX7-FKHD
ASPS	ASPSCR1–TFE3
Myxoid LPS	FUS-CHOP
EMC	EWS1R–CHN TAF2N–CHN TFG–NR4A3
DSRCT	EWS-WT1
SS	SYT-SSX
Clear cell sarcoma	EWS-ATF1
Angiomatoid MFH	TLS–ATF1 EWS1R–CREB1 EWS1R–ATF 1
DFSP	COL1A1–PDGFB
Myxoinflammatory fibroblastic sarcoma	Amplification of VGLL3
Well differentiated LPS	Amplification of MDM2, CDK4, HMGA2
Low-grade fibromyxoid sarcoma	FUS–CREB3L2 FUS–CREB3L1

The findings of this review show that for the primary workup of STTs, FNAC has several major advantages that certainly outweigh its limitations. However, the inexperience of cytopathologists with the wide spectrum of soft tissue neoplasms, coupled with overlapping morphologic appearances of reactive and neoplastic lesions, limit the widespread usage of FNAC as the diagnostic procedure of choice in STTs. In addition, there are still some rare STTs that can't be accurately diagnosed by FNAC because the cytological criteria that allow their correct diagnosis as benign or malignant, as well as to type them, have not been well established. However, FNAC in conjunction with ancillary studies (IHC, cytogenetics, flow cytometry, EM and cytogenetic analysis), along with the clinical and/or radiographic data can approach a diagnostic accuracy of 95% for the diagnosis of STTs. Although accurate assessment of the grade of STS is difficult by FNAC, yet if one is able to place the sarcoma into one of the five cytomorphological group (pleomorphic, spindle, myxoid, small round/ovoid, epithelioid) then a specific grade is not needed for the initiation of treatment because in most cases, the histological grade is readily apparent. However, subtyping spindle cell sarcomas as well as lipomatous tumors is often

challenging. The use of IHC is mandatory for proper diagnosis of these tumors.

So, this review assures the role of FNAC in the primary diagnosis of STTs as well, in recurrent and metastatic lesions. Exhaustive trials for subtyping and grading of some confusing STTs and the probability of error have to be weighed with the option of placing such tumors in one of the cytological groups which is a trend widely accepted by many authors.

5. Recommendations

Based on the results obtained from the present study, recommendations those worth mentioning are:

- Any patient with a STT presenting with any of the followings should be referred to a multidisciplinary musculo-skeletal centre: subcutaneous tumors larger than 5 cm in diameter, any deep-seated (inter- or intramuscular) tumors and any STT clinically suspected for malignancy.
- On performing FNAC from a STT, sampling tissue from at least three different parts from the tumor is advisable to assess its heterogeneity.
- The microscopic evaluation of STTs obtained by FNAC should be based on both wet fixed H&E or Pap stain and air-dried MGG stain.
- Small, deep seated STTs are to be needled with ultra sound guidance to avoid misdiagnosing reactive cellular changes as STS.
- On evaluating the cytological smears from STTs, it's recommended to place the STT into one of the five major cytomorphological subgroups based on the predominant cytological appearance: pleomorphic, spindle cell, myxoid rich, small round/ovoid cell and epithelioid cell. This aids in reaching a confident diagnosis of benignity or malignancy and suggesting a type-specific diagnosis.
- Optimal interpretation of cytology findings of STTs requires a combination of the results of ancillary studies (IHC, flow cytometry, cytogenetic analysis and EM), along with the clinical and/or radiographic data. Close interaction between the clinician and cytopathologist is therefore an essential component to the success of FNAC in the workup of STTs. The patient referral request should include full personal data, clinical data including site and size of the tumor, results of radiographic studies, previous biopsies if done, its result and detailed information concerning biopsy sites.
- Further correlative cytological-histological studies on large number of cases should be carried out to try to identify distinguishing cytological features for each type of STTs.
- Further scope of STT evaluation on cytology can be expanded with more studies dealing with application of ancillary techniques on aspirate samples.

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