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Malignant Fibrous Histiocytoma: Histopathological and Immunohistochemical Study

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Abstract

Malignant fibrous histiocytoma (MFH) is the most common soft tissue tumor in adult. It is generally regarded as arising from primitive mesenchymal cells that show partial histiocytic and fibroblastic differentiation. Immunohistochemical observations suggest that the expression of smooth muscle markers in the so called MFH is a result of myofibroblastic differentiation. The present study is aimed to correlate between histipathological subtype and clinical parameters, to grade the MFH cases depending on the histopathological criteria for grading, and to examine the cases immunohistochemically for myofibroblastic differentiation using smooth muscle markers in cases of MFH as an aid for accurate diagnosis. This study including 26 soft tissue specimens diagnosed as MFH collected from private and governmental histopathological laboratories in Basrah during the period from January 2000 to October 2005. Additional 4 cases (one leiomyoma, two fibromas and one fibrosarcoma were taken as control positive and negative. Twenty cases of MFH (77%) were in the age group 45-60 years. The mean age was 53.5 year with male to female ratio of 1.3: 1. Nineteen cases (73%) were located in the extremities mainly the lower limbs. Seventeen cases (65.4%) were primary. Twenty two (84.8%) were of pleomorphic subtype, two were myxoid and 2 were inflammatory. All the recurrent cases were regarded as grade III, from the seventeen primary cases fourteen were of grade III, so twenty three cases (88.5%) were of grade III, the remaining 3 cases were of grade II. No grade I tumor was recorded. The majority of pleomorphic subtype cases (95.5%) were of grade III. Both cases of myxoid subtype were of grade II. Desmin expression was found in only 3 cases (11.5%), none for smooth muscle actin or S-100 protein. There was no correlation between desmin expression and tumor site, subtype or grade, as well as, with age and sex of the patients. A strong association between desmin expression and recurrent tumors 33.3% was found.

Keywords: Malignant Fibrous Histiocytoma; Desmin; Myofibroblastic Differentiation; Primitive Mesenchymal Cells

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Introduction

The term "soft tissue" is used to describe any nonepithelial tissue other than bone, cartilage brain and coverings, hematopoietic cells, and lymphoid tissue. Soft tissue tumors (STT) are generally classified on the basis of type of tissue they arise from (Supplementary I) [1].

Supplementary I: Types of soft tissue tumor (STT).

Soft tissue type	Soft tissue tumors
Tumors of adipose tissue	Lipoma. Lipoblastoma Liposarcoma.
Tumors of fibrous tissue	Fibromatosis. Giant cell fibrobastoma Fibrosarcoma.
Tumors of skeletal muscle	Rhabdomyoma. Rhabdomyosarcoma.
Fibrohistiocytic tumors	Fibrous histiocytoma. Dermatofibrosarcoma protuberance. Malignant fibrous histiocytoma.
Tumors of smooth muscle	Leiomyoma. Leiomyosacroma. Smooth muscle tumors of uncertain malignant potential.
Vascular tumors	Hemangioma. Glomus tumor. Lymphangioma and Lymphangiomyoma Hemangioendothelioma. Hemangiopericytoma. Angiosarcoma.
Peripheral nerve tumors	Neurofibroma. Schwannoma. Perineuioma. Malignant peripheral nerve sheath tumors.
Tumors of uncertain histogensis	Granular cell tumor. Synovial sarcoma. Alveolar soft part sarcoma. Epitheliod sarcoma. Clear cell sarcoma of tendons and aponeuroses. Giant cell tumor of soft part. Desmoplastic small cell tumor.
Iumors of pleuripotential mesenchyme Tumors of metaplastic mesenchyme	

Soft tissue tumors (STT) either benign discovered incidentally or due to mass effect, or malignant ones called soft tissue sarcomas (STS), with aggressive local growth and wide spread metastasis. There is an

intermediate tumor with aggressive local growth but no metastasis. Sarcomas in general are uncommon, accounting for less than 2% of all malignancies [1]. The degree of differentiation is reflected by histologic grade, size, anatomic extent. The stage of tumor influences the biologic behavior of malignant soft tissue tumors [1]. It seems increasingly evident that tumors in fibrous histiocytic group (particularly the malignant ones) do not represent a specific type but rather a common pathway for a variety of other (STT), including fibrosarcoma, leiomyosarcoma, liposarcoma and others [2,3]. Immunohistochemical observations of neoplastic cells suggest that the expression of smooth muscle markers in the so called MFH is a result of myofibroblastic differentiation [4].

Malignant fibrous histiocytoma (MFH), also named as fibrohistiocytic sarcoma, it has been regarded as the most common malignant neoplasm of mesenchymal soft tissue of adult, accounting for approximately 20%-25%. Male and female affected equally with a peak incidence in the ages of 50-70 years. MFH is highly aggressive that often recurs locally and metastasizes in about 50% of patients. This tumor is composed of a dual cellular composition, cells with a fibroblastic appearance are intimately admixed with others having some of the morphological and functional characteristics of histiocytes [1-4]. The tumor is usually large grayish white and encapsulated mass that appear deceptively circumscribed despite their infiltrative growth at the microscopic level. It is usually soft to firm with areas of calcification, haemorrhage and necrosist [5,6]. MFH comes in more than 6 different varieties. The resemblance of MFH to a wide variety of other tumors make the differential diagnosis lengthy. "Pleomorphism", which means variation in cytoplasm and nuclear sizes and shapes of cells throughout the tumor, is an outstanding feature in MFH. Whereas other tumors such as liposarcoma and rhabdomyosarcoma, although exhibit pleomorphism, they tend to, do so within the constraints of their phenotype (i.e., they still look like the cells of origin) [4,7, and 8].

The microscopical picture depends on histologic subtype. In general, the cell has voluminous cytoplasm that may be pale to highly eosinophilic and occasionally vaculated. Importantly, the cytoplasm does not have agranular or fibrillary appearance of Rhabdomyoblast, however it may be vaculated, simulating a lipoblast. The cells of MFH may reach large to huge size. The nucleus is bizarre with many lobes of differing sizes with prominent nucleolus. The nucleus has thick nuclear membrane and exhibit a jagged outline that may be "irregularly irregular", with occasional inclusions or vaculations. The huge bizarre cells exist in practically all examples of MFH (exceptions are the rare angiomatoid and inflammatory variants) [9-11].

The presentations of patient with MFH are similar to most of other sarcomas including mass effect or metastasizing features [1,2, and 10]. However, patient with inflammatory subtype of MFH may experience generalized signs and symptoms as fever, leukocytosis and elevated serum granulocyte colony-stimulating factor (G-CSF) concentration. The inflammatory reactions subside immediately after tumor resection, strongly suggesting that the primary tumor cells produce G-CSF [10].

MFH may virtually occur at any site of the body including the visceral organs, however, the lower extremities is the most common site "particularly the thigh". It also occurs frequently in reteroperitonial soft tissues. In the bone it accounts. for about 1% of malignant tumors and frequently in the metaphysis of long bones [2-4]. Other reported locations include head and neck (5-15)%, orbit, oral cavity and brain [12]. In the GIT tract, MFH is extremely rare [13], it also reported in the pancreas [14], mesentery to date up to 28 cases were reported, and even in the gall bladder [15]. In the breast MFH reported as the mesenchymal component of sarcomatoid carcinoma [16]. Another rare locations include aortic bifurcation [17], heart, spermatic cord to date up to 43 cases were reported [18]. In the skin MFH occur in sun exposed areas [19]. In the kidney there is strong predilection for local recurrence and poor prognosis [20].

MFH Variants

A typical fibroxanthoma

It is the superficial type of MFH. Like deep forms of MFH, pleomorphic cells are apparent at low power together with small cells and cells with angulated and curved nuclei, along with inflammatory infiltrate. The immunoprofile is similar to other types of MFH [21].

Storiform-pleomorphic MFH

Is the prototypic and most common of MFH member accounting for 66%-77% with a peak in the seventh decade. Some appear around an infarct, foreign body, and surgical scar or at the site of previous radiation. It develops in the deep soft tissue and reaches a large size with possible cystic changes and areas of necrosis. The presence of highly pleomorphic tumors cells and a storiform pattern of growth are the two most important diagnostic features. Numerous hyaline globules of variable sizes may be present in the cytoplasm of giant cells. Inflammatory infiltrate (other than neutrophilic), metaplastic bone or cartilage may be present. This type has a high tendency to locally recur and distally metastasize. In this type tumor size and depth play an important prognostic role [1,3,4, and 8].

Myxoid MFH

Most of them occur in the extremities of adult person and usually attached to the fascia of the major muscles. It accounts for about (15-17)% with a peak in seven" decade, it has better prognosis. They are mucoid in appearance and resembling myxoid liposarcoma. It exhibits a number of histologic features distinguishing it from myxoid liposarcoma.

1. Pleomorphism is prominent,
2. The cells have a stellate or tripolar shape (like myofibroblasts).
3. The vessels are recognizably different, being thick-walled and often curved with a wide arc.

They are not isolated fine capillaries but, instead, have an eosinophilic substance associated with them and adherent tumor cells adding to their thick appearance in low power. This type is distinguished from liposarcoma by the presence, elsewhere in the tumor, of typical areas of MFH in the absence of true lipoblasts. Myxoid MFH should contain greater than 50% myxoid histology and, therefore, the fourth differentiating feature is the presence of myxoid component that is of proteoglycan nature with alcian-blue positive, and oil red-O stain negative nature of histochemical analysis [1,4, and 8].

Inflammatory MFH

This type is most commonly occur in the retroperitoneal areas, it is highly aggressive type accounting for about (3-5)%. It is the same as the classical subtype. This tumor has bizarre neoplastic cells, which are admixed with an intense inflammatory infiltrate rich in neutrophiles. Storiform pattern, collection of foamy cells and areas of necrosis are e constant features. When the inflammatory infiltrate rich in lymphocytes or plasma cells this will be regarded as lymphocyte- rich inflammatory

MFH. Patient with this type has an elevated C- reactive protein level and associated peripheral leukemoid reaction and eosinophilia, this can be a useful prognostic indicator and a valuable marker for disease activity [1,3,8, and 22].

Angiomatoid MFH

It is a rare type appear in the extremities of children and young adults [1,4, and 9]. It is a circumscribed, multinodular, or multicystic hemorrhagic mass. It has highly cellular foci which are mixed with focal areas of hemorrhagic cyst-like spaces and large aggregates of chronic inflammatory cells which arranged at the periphery of the tumor as lymphoid follicles that may simulate a lymph node. It usually lacks pleomorphism as adominent feature and often exhibit immunoreactivity to CD68. This type is a low or an intermediate grade malignant tumor with diploid DNA content and only 2% of patients have died of metastatic disease [1,4, and 8].

Giant-cell type of MFH

This is a newly recognized subtype accounting for (3-15)% with average age of 56 year. It is called malignant giant-cell tumor of soft part. Microscopically numerous osteoclast-like giant cell are clearly visible which have marker expression of true histiocytes. These cells contain from 20 to 100 nuclei with similar small round to oval appearance. These cells are seen in a background of much smaller stromal cells with oval nuclei and frequent mitosis. The natural history of this type is similar to that of common type [1,3, and 8].

Immunohistochemistry

There are no specific markers for fibrohistiocytic tumors. Because of the low specificity of alphal-antitrypsin, alphal-antichymotrypsin, lysozyme and ferritin, these markers are no longer used [1,4].

Muscle markers stain some of fibrohistiocytic lesions, and these can be of advantage in limited situations. These markers are Desmin, Myoglobin, Muscle specific actine, Smooth muscle actin and Myogenin. Myogenin and Myoglobin are specific for skeletal muscle only. However, fibrohistiocytic and myofibroblastic tumors are frequently contain at least focal or sometimes diffuse reactivity for the remaining muscle markers. This may cause an erroneous diagnosis of Leiomyosarcoma if one were to depend on immunoprofile alone. The fact that some cases of MFH also contain desmin, might be explained by the presence of myofibroblasts ultrastructurally. Thus, if faced with a possible desmin positive MFH, one should consider MFH together with pleomorphic or dedifferentiated Leiomyosarcoma and take growth pattern and histologic features into account [23-27].

Calponin and h-Caldesmon, which are Cytoskeleton associated actin- binding proteins, have been reported to be more specific myogenic markers than Desmin, Smooth muscle actin and Muscle specific actine. These two markers are important distinguishing MFh with myofibroblastic differentiation [which has calponin (∓) and h-caldesmon (–) immunoprofile] from smooth muscle differentiation in Leiomyosarcoma [which has calponin (+) and h-caldesmon (∓) immunoprofile] [28].

Cytogenetic study

Few studies on cytogenetics in MFH was reported. In two studies chromosomal changes in the form of gain or amplification was shown to affect chromosomes 8q, 6q and 12q in MFH cases [29,30]. Also, there is a study shows that P53 (a tumor suppressor gene) mutation is involved in MFH cell proliferation [31]. Flowcytometric study of fibrohistiocytic tumors showed that only 40% of MFH have aneuploid chromosomal pattern, while the remaining have a diploid pattern. Therefore, while the aneuploid pattern certainly confirm the malignant type of fibrohistiocytic tumors, the diploid pattern may be either benign or malignant [32-34].

The most significant prognostic factors are grade, stage, P53 overexpression, MIB-1 proliferation index and proliferating cell nuclear antigen (PCNA) factor [1].

Materials and Methods

This study includes 26 soft tissue specimens diagnosed as MFH. These cases where collected from private laboratories. Ten cases were collected from histopathologic laboratory of Al-Basrah Teaching Hospital during the period from January 2000 to October 2005. Additional 4 cases (one leiomyoma, one fibrosarcoma and the remaining two fibroma) were included as controls.

The study includes:

1. Evaluation of the request information concerning the age and sex of patients, the site and presentation of tumor and correlative them with histopathological subtype of MFH.

2. Examination of paraffin embedded sections stained with Hematoxylin and Eosin (H & E) to determine the subtype of MFH.

3. Histopathological grading: including subtype of MFH, mitosis, cellularity, cellular pleomorphism and necrosis.

4. Immunohistochemical study for smooth muscle marker expression (Desmin, actin) and S-100 protein.

Staining Methods (Supplementary II): Hematoxylin and Eosin stain [35].

Supplementary II: Results of staining.

Nuclei	Blue
Muscle, keratin and elastic fibers	Bright red
Collagen and nerve fibers	Pink
Red blood cells	Orange

Solution: 1- Mayer's Hematoxylin. 2- Eosin solution (0.5%). 3- Differentiation: 1% hydrochloric acid in 70% alcohol.

Histological grading system

Histological criteria for grading MFH [36-39] depends on score (Supplementary III). Based on A and B the three grades are defined.

Supplementary III: Histological criteria for grading MFH depends on score [36-39].

Immunohistochemical staining: AII the cases of MFH and control examined immunohistochemically, using Desmin, Smooth

Supplementary III: Histological criteria for grading MFH depends on score [36-39].

Score A	Number of mitoses pr 10 HPF
Score B	Mean score (1, 2 or 3) based on semi quantitative evaluation of the following histological criteria:
a	Cellularity in relation to amount of stroma, result either 0 or 1.
	Low and moderate cellularity = 0
	Highly cellular =1
b	Cellular pleomorphism result usually 1.
c	Necrosis either 0 or 1.
	Abscent =0
	Present=1

muscle actin and S-100 protein for evaluation of myofibroblastic differentiation.

Desmin

It is a muscle type intermediate filaments (MW 55,000) are found in cells of smooth and straited muscle and also in myofibroblast. It is particularly abundant in paranchymal smooth muscle. Reactivity for Desmin but with negative expression for actin is one feature of myofibroblastic differentiation [1,4].

Actin

This is ubiquitous contractile protein responsible for cell motility. It is an extremely useful marker for the identification of smooth muscle cell and myofibroblast. Various isoforms of this protein exist, including those which are specific for smooth muscle and those for striated muscles called (sarcomeric) actin [1,4].

S-100 protein

This is a family of acidic, dimeric calcium-binding protein (MW 21,000) composed of different combination of alpha and beta subunits and first isolated from the central nervous system. They are present in the nucleus and cytoplasm of glial and schwann cells, melanocyte, chondrocytes, adipocytes, myoepithelial cells and in tumors derived from them. The wide expression of this antigen has substantially diminished its diagnostic utility. It's main use is in the evaluation of peripheral nerve sheath and melanocytic tumors [1,4].

Immunohistochemical staining protocol (BioGenix com.) scoring

The positive score of immunostaining was calculated as the number of cells with positive reaction divided by the total number of neoplastic cells. In each specimen, a minimum of 1000 neoplastic cells were analyzed [40-42].

Supplementary IV: Three grades are defined.

Grade I	<1 mitosis/10 Hpfwith score B= 1
Grade II	<1 mitosis/10 Hpfwith score B = 2 or 3
	or 1-5 mitoses/10 Hpf with score B= 1 or 2
Grade I	1-5 mitoses/10 Hpf with score B =3
	or > 5 mitoses / 10 Hpf with score B = 1, 2 or 3

Supplementary V: Immunohistochemical staining protocol (BioGenix com.)

1. Paraffin section using positive charged microscopic slide.
2. Section deparaffinized and rehydrated by graded alcohol then D. W.
3. Immerse sections in (Retrieval solution) citra (1 ml of concentrate +9 ml D. W) in water bath heated to 95°C for 10-20 min.
4. Cool sections to room temperature for 20 min.
5. Rinse sections in buffer and bathing 2-5 min.
6. Tap of excess buffer and wipe around sections by gauze pad and make a circle around section by PAP pen.
7. Apply enough Hydrogen peroxide to cover specimen for 5-10 min. blocking endogenous peroxidase.
8. Wash in D. W and then in buffer.
9. Tap of excess buffer and wipe around sections.
10. Apply enough powder block reagent 5-10 min.
11. Tap of excess blocking reagent only. (don't wash).
12. Apply enough primary antibodies diluted in common diluent

1. (Desmin, Actin, or S -100 protein) overnight in humid weather.

13. Wash in buffer and bathing 2 min.
14. Wipe around sections.
15. Biotinlated link (1:20 dilution) for 10-20 min.
16. Wash in buffer and bathing 2 min.
17. Wipe around sections.
18. Streptavidin-peroxidase complex for 10-20 min.
19. Wash in buffer and bathing 2 min. then wipe sections.
20. Substrate-chromogen solution (DAB) 5-15 min.
21. Wash with tap water.
22. Counter stain with hematoxylin 1-2 min.
23. Wash with tap water, without dehydration.
24. Mount with glycerin buffer solution.

Statistics

All data were analyzed by Statistical Package for Social Sciences version 24 (SPSS v24) (SPSS Inc., Chicago, Illinois, USA). The mean and standard deviation were used to describe continuous numerical data. Categorical data were presented by frequencies and percentages. Fisher exact test was used. A P-value equals to or less than 0.05 was considered significant.

Results

The total number of were 26 cases; 15 cases were male and 11 cases were female. The male to female ratio was 1.3:1. The ages were range from (22-85) years with a mean age of (53.5) year. However, 20 cases (77%) were in the age group from (45-60) years (Table 1).

Table 1: Demographic distribution of MFH patients.

Age (years)	Sex		Total	%
	Male	Female		
<30	1	-	1	3.9
44-31	2	1	3	11.5
60-45	12	8	20	77
>61	-	2	2	7.6
Total	15	11	26	100
%	57.6	42.4	100	

Seventeen cases (65.4%) presented for the first time (i.e., primary), while the remaining nine cases (34.6%) were recurrent tumors. Of the primary cases only two were of Myxoid subtype, two inflammatory and 13 were pleomorphic. All recurrent cases were pleomorphic subtype of MFH (Table 2).

Tumors located in the extremities were 19 cases; 15 were in the lower limbs and 4 were in the upper limbs upper to lower ratio is 3.7: 1. All lower limb MFH cases were of pleomorphic subtype, while in the upper limb two cases were of pleomorphic subtype and 2 were of myxoid. The remaining 7 cases were located in the trunk, 5 in the chest

Table 2: Correlation between presentation and tumor subtype.

Histological subtype	Presentation				Total	%
	Primary	%	Recurrent	%		
Storiform pleomorphic	13	76.4	9	100	22	84.8
Myxoid	2	11.7	0	0	2	7.6
Inflammatory	2	1.7	0	0	2	7.6
Total	17	100	9	100	26	100
%	65.4		34.6		100	

wall and were of pleomorphic subtype, 1 in the anterior abdominal wall and 1 in the retroperitoneum and both were of inflammatory subtype (Table 3).

Table 3: Correlation between site and histological subtypes.

Histological subtype	Presentation				Total	%
	Extremeties no.	%	Recurrent	%		
Storiform pleomorphic	17	89.4	5	100	22	84.8
Myxoid	2	10.5	0	0	2	7.6
Inflammatory	0	0	2	0	2	7.6
Total	19	100	7	100	26	100
%	73		27		100	

The recurrent cases were considered to be of grade III, for the primary cases and depending on the histopathological grading criteria, from the seventeen primary cases fourteen were of grade three so 23 cases out 26 cases (88.5%) were of grade III. The remaining 3 cases were of grade II. According to histological subtype of MFH, 21 cases out of 22 cases of with pleomorphic subtype were grade III (95.5%); one case was grade II. Both Myxoid subtype cases were grade II, while both inflammatory subtype cases were grade III. No grade I tumor was recorded (Table 4).

Table 4: The relation between histological subtype and grade of MFH cases.

Histological subtype	Presentation				Total	%
	II		III			
	No.	%	No.	%		
Pleomorphic	1	33.3	21	91.3	22	84.8
Myxoid	2	66.6	0	0	2	7.6
Inflammatory	0	0	2	8.7	2	7.6
Total	3	100	23	100	26	100
%	11.5		88.5		100	

Tumor cells were considered positive if definite staining from faint to strong staining distant from the edge of the section or areas of necrosis was observed. The slides were considered positive when > 1% of the cells were stained [42]. The extent of immunostaining in each specimen was scored by two independent observers according to the number of stained tumor cells (Figure 1).

S-100 protein staining: None of the 26 studied cases have shown reactivity for this marker.

Smooth muscle actin staining: No cases have shown reactivity for this marker.

Desmin staining: Three cases out of 26 cases of MFH 11.5% showed immunoreactivity for this marker (i.e.: myofibroblastic differentiation). Of these 3 positive cases, two showed 10% of malignant cells had Desmin staining and one case had 15% of the cells positive.

Relation between Desmin immunoreactivity and clinical presentation (Table 5). All the three positive cases for Desmin were recurrent. From statistical point of view, there is significant association between recurrence and myofibroblastic differentiation.

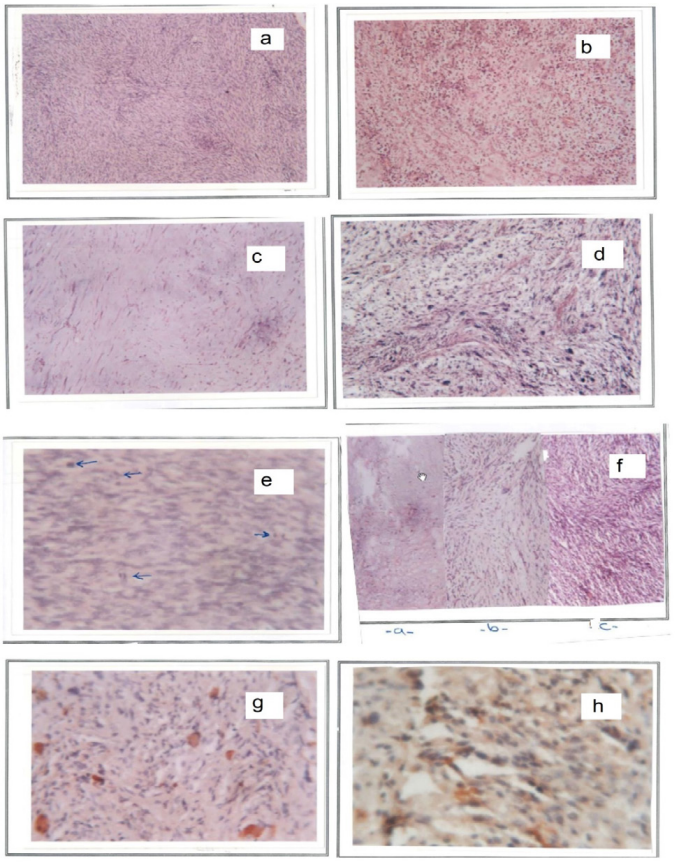

Figure 1: a. The storiform pleomorphic subtype of MFH. X 100(H&E); b. The inflammatory subtype of MFH. X 100(H&E); c. The myxoid subtype of MFH. X 100 (H&E); d. The high cellular anaplasia (pleomorphism). X 400 (H&E); e. Mitosis in MFH cases. X 400 (H&E); f. Degrees of cellularity a- Low b- Moderate c- High. X 100 (H&E); g. and h. Positive cytoplasmic staining for Desmin. X 400 (desmin).

Table 5: The relation between Desmin expression and clinical presentation.

Presentation	Negative expression		Positive expression		Total	
	No.	%	No.	%	No	%
Recurrent	6	26	3	100	9	34.6
Primary	17	74	0	0	17	65.4
Total	23	100	3	100	26	100

X^2=6.42; P value < 0.05; d=l

Desmin reactivity was shown in two male cases and one female case (Table 6). From statistical point of view, there is no significant association between sex of the patient and myofibroblastic differentiation.

Table 6: The relation between Desmin expression and sex.

Sex	Negative expression		Positive expression		Total	
	No.	%	No.	%	No	%
Male	13	56.5	2	66.6	15	57.6
Female	10	43.5	1	33.4	11	42.4
Total	23	100	3	100	26	100

X^2= 0.092; P value > 0.05; df=l

Relation between histopathological grade of the tumor and Desmin immunostainin (Table 7). From statistical point of view, there is no

Table 7: The relation between Desmin expression and grades.

Grade	Negative expression		Positive expression		Total	
	No.	%	No.	%	No	%
II	3	13	0	0	3	11.5
III	20	87	3	100	23	88.5
Total	23	100	3	100	26	100

X^2= 0.018; P value > 0.05; df=1

significant association between grade of the tumor and myofibroblastic differentiation.

Discussion

Malignant fibrous histiocytoma (MFH) is regarded as the most common malignant neoplasm of mesenohymal soft tissue. In a study done in Basrah by AL-Wiswasy MK, et al. (1999) [43], the incidence was (14.8%) and it was the third most common tumor after fibrosarcoma and rhabdomyosarcoma. It designates a spectrum of tumors that allow their inclusion in distinct clinicopathologic setting, although being not uniform in their histogenesis and pathogenesis [1,4].

The present study showed that 2 cases (7.6%) were located between 40-44 years and 20 cases (77%) were at the age group between 45-60 years so the high percentage of tumor occurs at the fifth and sixth decades of life, constitutes (84.6%) of the total number of cases. The mean age was 53.5 year. Belal A, et al. (2002) [44], in his study at Saudi Arabia and Okuno S, et al. (2002) [45], in a study done at Mayo clinic found approximating results to this study, the mean ages were 48 and 50 years respectively.

The male to female ratio in this study was 1.3:1. Rööser B, et al. (1991) [46], founded a ratio of 1:1 in his study. On the other hand, Gebhard S, et al. (2002) [47], in a study on 63 cases of MFH showed a ratio of 2.2:1, AL-Wiswasy MK, et al. (1999) [43], found a ratio of 2.2:1.

In the present study 73% of cases were located in the extremities mainly the lower limbs upper to lower ratio 3.7:1. Similarly Weiss SW, et al. (1978) [48], in study done in England showed that 70% of the studied cases were located in the extremities. Engellau J, et al. (2004) [49], and Bertoni F, et al. (1985) [50], in a study done in US were showed that around 80% were located in the extremities.

This study showed that (84.8%) of the studied MFH cases were of oriform-pleomorphic subtype. Kearney MM, et al. (1980) [51], in a study done in Australia showed that this subtype account for 75% of the 167 studied MFH cases.

Both of inflammatory subtype cases were trunkal in location, one was roperitonial and the other was in the anterior abdominal wall. Kyriakos M, et al. (1976) [52], in a study done in Korea on 30 cases of inflammatory subtype founded that 80% of these cases were trunkal in location.

All the recurrent cases were not included in grading system but rded from the start as grade III. According to the grading criteria for only primary cases 14 were of grade III, so the total number of cases with II account for (88.5%). Peiper M, et al. (2004) [53], and Hasegawa T, et al. (2002) [54], in Japan showed in their studies that MFH is usually a high grade tumor (i.e. 85% of grade III).

Twenty one cases out of 22 pleomorphic subtype cases (95.5%) were de III. This is in agreement with Engellau J, et al. (2004) [49], study in US state showed that 97% of storiform-pleomorphic subtype MFH cases were of grade III.

On the other hand, both myxoid subtype cases were of grade II tumor, while inflammatory subtype cases were of grade III. Costa J, et al. (1984) [36], and Myhre-Jensen O, et al. (1983) [37], in a study done in Scandinavian countries showed that myxoid subtype cases were usually of grade II but inflammatory subtype cases were either of grade II or grade III.

In the present study 3 cases out of 26 MFH cases (11.5%) were shown positive expression for desmin, none for smooth muscle actin and S-100 protein. Similar results were reported by Ueda T, et al. (2003) [55], in Japan who showed that only 9% of his studied cases had positive desmin expression but none fore smooth muscle actin. Joo M, et al. (2003) [56], in China showed that none of the studied MFH cases had reactivity for desmin, smooth muscle actin and S-100 protein.

In a study of 100 cases of soft tissue MFH, Hasegawa T, et al. (2003) [10], in Japan showed that 17% of cases had positive expression for desmin, 3% of the cases had positive expression for smooth muscle actin but none for S-100 protein.

The differences in the result may be due to so many causes as differences in the sample size among different studies or due to the fact that differing sources of antibodies may cause the discrepancy in varying results), or it was well known fact that desmin reactivity is highly affected adversely by formalin fixation". Or may be explained on the bases that immunoreactivity for desmin is variable and is particularly dependent on tumor site, tumors in soft tissue appear to contain less immunoreactivity than other site, or due to the fact that MFH of bone derives from mesenchymal stromal cells in bone marrow and has a more myofibroblastic differentiation than soft tissue MFH [55].

In the present study the 3 cases with positive immunostaining for desmin [i.e., Myofibroblastic differentiation] were recurrent, from statistical point of view there is significant association between recurrence and otherline of differentiation of the primary tumor (P value < 0.05).

This positivity for desmin but negativity for actin is one feature of myofibroblastic differentiation. This does not mean infiltration of tissue muscles at the site of recurrence because it should be positive for actin also, this could be confirmed by using of more specific myogenic markers which are calponin and h-caldesmon. Myofibroblast has calponin (∓) but h-caldesmon (-) immunoprofile but muscle differentiation has calponin (+) and h-caldesmon (∓) immunoprofile [28].

This is in agreement with what Gazziola C, et al. (2003) [57], in a study done in Italy who concluded from their studies that most cases with positive smooth muscle marker or other marker expression i.e., other line of differentiation for MFH occur mainly in recurrent tumors. This may be explained by the morphologic modulation resulting from tumor progression.

In this study there is no significant association between desmin expression and grade or histological subtype of the tumor, also no significant association between desmin expression and patient sex. This is in agreement with Hasegawa T, et al. (2003) [10], study.

Conclusion

MFH is a common tumor of mesenchymal soft tissues affecting mainly the lower extremities of elderly people. MFH is usually a high-grade sarcoma and mainly of storiform- pleomorphic subtype. In some cases of MFH, desmin reactivity might be explained by the presence

of myofibroblastic differentiation. There was no correlation between grade of MFH cases and desmin expression. There was no correlation between tumor subtype or site and patient's sex with desmin expression. There was strong association between clinically recurrent tumors with myofibroblastic differentiation in the form of desmin expression.

Recommendation

Further studies are recommended for desmin positive MFH cases, they are as follow: Immunohistochemical study of more specific muscle markers such as calponin and H-Caldesmon. Electron microscopic examination of substructural features of myofibroblastic differentiation. Cytogenetic study for "MFH specific" genes.

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