Journal of Integrative Oncology
ISSN: 2329-6771

Research Article Open Access

PTEN in Primary Malignant Fibrous Histocytoma: Clinical, Histologic and Prognostic Correlations

Manal Mohamed Zyada, Mohamed Ibrahim Mourad*, Heba Mahmoud Elsabaa and Mahitabe Elgamily

Department of Oral Pathology, Faculty of Dentistry, Mansoura University, Mansoura, Egypt

Abstract

Phosphatase and Tensin Homolog (PTEN) is a protein that is encoded by the PTEN gene. Mutations of this gene are a step in the development of many cancers. A decrease or loss of PTEN expression has been described in many types of malignancies. This study was designed to evaluate by immunohistochemistry the relationship of Phosphatase and Tensin (PTEN) homolog expression and clinicopathological parameters of thirty-two archival tumor tissues of Malignant Fibrous Histocytoma (MFH) patients as well as analyzing the relationship of its expression with response to therapy. Hematoxylin and eosin-stained sections from 32 MFH cases were classified according to well-defined criteria into 4 groups. Then, they stained immunohistochemically with PTEN protein. Quantitation of immunoreactivity was performed using an Olympus light microscope interfaced via a Sony camera to an image analysis system. The tendency was observed for positive PTEN expression to be associated with both storiform and giant cell subtypes. Moreover, the loss of PTEN in the 10 patients with recurrent disease who underwent salvage chemotherapy had a poor response to chemotherapy. The present study has demonstrated that loss of PTEN may serve as a reliable biological marker of high malignancy potential in of malignant fibrous histiocytoma. Moreover, loss of PTEN is an important event in regulating sensitivity to chemotherapy in those cases. Thus, our results suggest that the PTEN gene may be a therapeutic target for the treatment of malignant fibrous histiocytoma PTEN MFH cases and its expression help to predict the treatment response.

Keywords: MFH; PTEN; IH; Treatment options

Introduction

Phosphatase and Tensin homolog (PTEN) is a protein that, in humans, is encoded by the PTEN gene [1]. Mutations of this gene are a step in the development of many cancers. PTEN acts as a tumor suppressor gene through the action of its phosphatase protein product. This phosphatase is involved in the regulation of the cell cycle, preventing cells from growing and dividing too rapidly [2]. It located on chromosome 10q23.3 and encodes a cytoplasmic protein that controls cellular processes, such as cell cycling and apoptosis 3-kinase [3]. A decrease or loss of PTEN expression has been described in many types of carcinomas and other malignancies [4-6]. Moreover, its negative prognostic value has been proven in many types of cancer. Studies in bladder, colon and ovarian cancers indicated a correlation between defective PTEN and resistance to chemotherapy [6-8].

Malignant Fibrous Histiocytoma (MFH) is the most common malignant soft tissue tumor in adults [9]. Histopathologically; MFHs can be sub-classified as storiform, pleomorphic, myxoid, giant cell, and inflammatory types [10]. The most important prognostic factor for MFH is the stage of the tumor. The stage is determined by tumor grade, size, depth, and presence of metastasis, and is a function of mitotic rate and tumor necrosis [11-13]. In MFH, the expression profile of the PTEN is poorly defined and its significance is uncertain. We aimed to investigate the relationship of PTEN expression and clinicopathological parameters of MFH patients as well as analyzing the relationship of its expression with response to therapy.

Materials and Methods

Pretreatment clinical examination was done to every case. A minimum follows up period of 7 months was considered to all cases after finishing their treatment to assess their clinical response.

Population

From 1995 to 2016, 40 patients with MFH and no evidence of dissemination at the time of diagnosis were seen and treated at Clinical Oncology Outpatient Clinic, Mansoura University. Histopathological material from the original tumor was available in 32 cases. The available clinical data regarding the age at diagnosis, sex, duration of symptoms before diagnosis, tumor size and location, local extension, therapy, and follow-up were noted.

Histopathology

The hematoxylin and eosin-stained sections from all thirty-two patients were reviewed by two observers. All tumors were fixed in 10% neutral buffered formalin and the tumors were classified according to well-defined criteria [14].

Immunohistochemical analysis

Paraffin-embedded, 4-µm thick tissue sections from the thirty-two MFH were stained for the PTEN protein using a primary rabbit polyclonal anti-PTEN antibody (Zymed Laboratories, San Francisco, Calif). De-paraffinization of all sections was performed through a series of xylene baths, and rehydration was performed through graded alcohols. The sections were then immersed in methanol containing 0.3% hydrogen peroxidase for 20 min to block the endogenous peroxidase activity and were incubated in 2.5% blocking serum to reduce nonspecific binding. Sections were incubated overnight at 4°C with primary

***Corresponding author:** Mohamed I Mourad, Department of Oral Pathology, Faculty of Dentistry, Mansoura University, Mansoura, Egypt, Tel: +201117901705; E-mail: drmourad11@yahoo.com

Received February 05, 2019; **Accepted** February 21, 2019; **Published** February 29, 2019

Citation: Zyada MM, Mourad MI, Elsabaa HM, Elgamily M (2019) PTEN in Primary Malignant Fibrous Histocytoma: Clinical, Histologic and Prognostic Correlations. J Integr Oncol 8: 226.

anti-PTEN antiserum (1:100). The sections were then processed using avidin-biotin immunohistochemical analysis according to the manufacturer's recommendations (Vector Laboratories, Burlingame, Calif). Diaminobenzidine was used as a chromogen, and commercial hematoxylin was used for counterstaining. Adjacent normal-appearing epithelium within the tissue sections served as a positive internal control. A case of colon carcinoma was included as a positive external control. Slides in which the primary antibody was omitted served as negative controls.

Staining assessment

Quantitation of immunoreactivity was performed using an Olympus light microscope interfaced via a Sony camera to an image analysis system (QwinPro, Leica and Wetzlar, Germany). The percentages of PTEN immunopositive cells were obtained from 20 random fields per case/section using a 10X objective lens. Estimation of PTEN immunostaining intensities was made in immune-positive cells also was made. Tumor cells immunoreactivity was scored as follows: (–)=100% of cells were negative, mild (+)=(0%–<25%) of cells were positive, moderate (++)=(25%–>50%) of cells were positive and intense (+++)=(75%–100%) of the cells were positive. The staining intensity in PTEN-positive cases was verified as strong and weak.

Strong: densely stained reaction visible at low magnification (objective 4X).

Weak: faintly cytoplasmic reaction visible at higher magnification.

Treatment response

Treatment included surgical ablation followed by postoperative radiation therapy (12 of 32), surgical ablation only (16 of 32), surgical ablation combined with radiation therapy and chemotherapy (4 of 32).

For patients with local recurrences and distant metastases, the objective response to salvage chemotherapy was evaluated by using well-defined criteria [15]. A complete response represented a complete disappearance of this tumor, while a partial response was represented by a 50% decrease in tumor size. The response rate was based on radiological and/or pathological findings.

Statistical analysis

Because of the relatively small sample size, Fisher exact tests were exclusively used to examine associations between categorical variables. $P<0.05$ was considered statistically significant.

Results

Clinical and pathological features

Patients' age ranges from 38 to 78 with a mean age of 59.96 years. There was a distinct female predilection among study cases with a female to male ratio of 3:1 respectively. In relation to the site, the majority of the cases were within maxilla (25% of all cases). Of the 32 tumors, 62.5% were large and exceeded 3 cm in diameter.

Distant metastasis to the lung occurred in four patients while local metastasis to regional lymph nodes was demonstrated in eight patients. Recurrence was recorded in 20 patients. Local recurrence in patients treated with surgical ablation combined with adjuvant therapy was lower than that in patients treated with surgical ablation only with a ratio of 1:4 respectively. Moreover, large tumors showed higher local recurrence than small lesions.

Twelve patients (37.5%) remained free of disease for more than 1 year after diagnosis. Moreover, only two patients died immediately 4 months after diagnosis, because of local recurrence and distant metastases.

The most common histological variant within the studied cases was the storiform-pleomorphic (62.5%). The giant cell type was detected in eight cases (25%), while only four cases were of the inflammatory variant. The giant cell variant was associated with a good prognosis and respond well to surgical ablation. The storiform-pleomorphic and the inflammatory subtypes were more aggressive and respond to surgery alone with a lesser extent.

Immunohistochemical staining

Regarding immune-reactivity, the staining was cytoplasmic. Loss of PTEN expression was noted in twenty (62.5%) of the thirty-two MFH cases. Weak expression was seen in only four cases (12.5%). The remaining eight cases (25%) revealed strong PTEN immune-positivity (Figures 1-4).

The correlation of the immune-staining with different clinic-pathological parameters in MFH is shown in Table 1. Although a tendency for positive PTEN expression was observed to be associated with smaller tumors and was more likely to be present in patients younger than 60 years. No relationship was observed between the PTEN immune-staining in one hand and age as well as both sex and site of tumor on the other hand. However, a tendency for positive PTEN expression was observed to be associated with both storiform and giant cell subtypes, there was no statistically significant difference between PTEN expression and histological subtypes of MFH.

Of the twenty patients whose tumors were PTEN negative, sixteen (80%) had a recurrence at follow-up, whereas only four cases of the twelve patients whose tumors were PTEN positive had a recurrence (Table 2).

The results of immunohistochemical staining for PTEN and its relationship to the objective response to salvage chemotherapy treatment

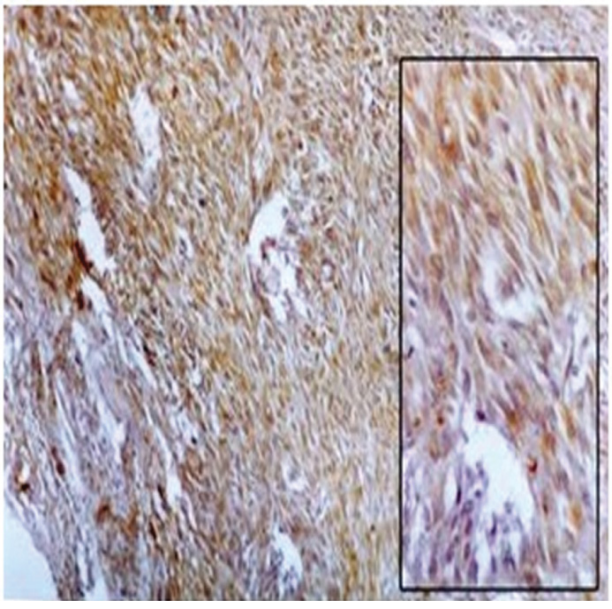

Figure 1: MFH (Storiform-pleomorphic type) shows diffuse intense positive cytoplasmic reaction to PTEN in many neoplstic cells in the storiform area. Inset shows higher magnification of immuno-reactive cells (ABC DAB 100X).

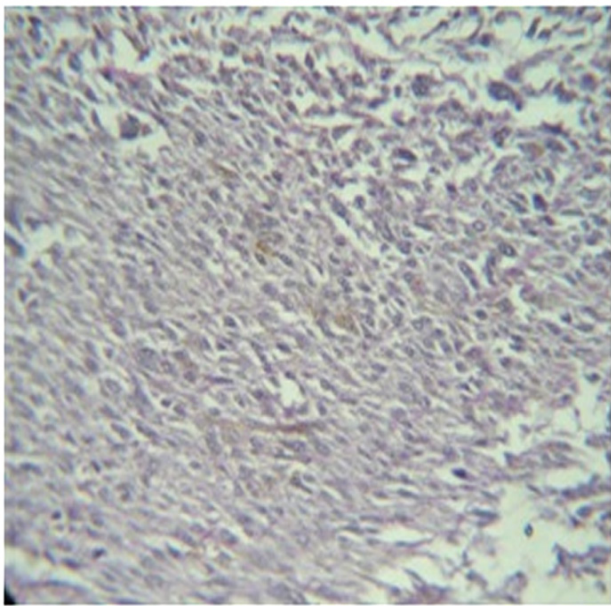

Figure 2: MFH (pleomorphic type) shows mild positive cytoplasmic reaction to PTEN in some neoplstic cells (ABC DAB 100X).

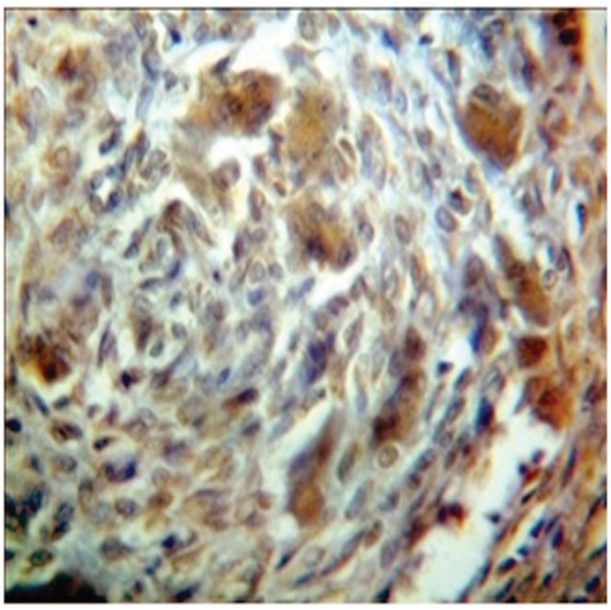

Figure 3: MFH shows strong positive cytoplasmic reaction to PTEN protein in many spindle cells with storiform pattern and an admixture of histiocyte-like cells with prominent pleomorphism, hyperchromatism and frequent mitotic figures and bizarre multinucleated giant cells (ABC DAB 400X).

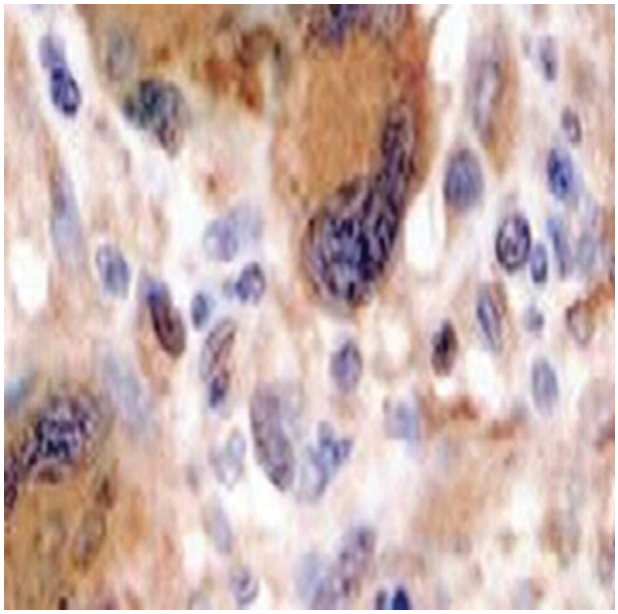

Figure 4: MFH (giant cell type) shows strong positive cytoplasmic reaction to PTEN protein in stromal and multinucleated giant cells (ABC DAB 400X).

Parameter	No. of cases	Positive PTEN immuno-staining	p-value
Age			
<60	20	12 (60%)	NS
>60	12	0 (0%)	
Sex			
Female	24	4 (16.7%)	NS
Male	8	8 (100%)	
Site			
Maxilla	8	4 (50%)	
Mandible	2	2 (100%)	
Buccal mucosa	6	0 (0%)	NS
Tongue	4	2 (50%)	
Lips	4	2 (50%)	
Soft palate	4	0 (0%)	
Floor of the mouth	4	2 (50%)	
Tumor size			
<3 cm	12	4 (33.3%)	NS
≥ 3 cm	20	8 (40%)	
Histological subtype			
Storiform-pleomorphic	20	8 (40%)	
Giant cell type	8	4 (50%)	NS
Inflammatory type	4	0 (0%)	
NS: Not significant			

Table 1: Relationship between PTEN immuno-staining and clinicopathological parameters in malignant fibrous histiocytoma.

are summarized in Table 3. Partial response of only four cases of the twenty tumors with negative staining to chemotherapy was detected while eight tumors with positive staining responded. Statistically, there was no significant association between PTEN immuno-staining and response to salvage chemotherapy.

Discussion

MFH can arise from soft tissue or bone. Their occurrence is most common in the soft tissues of the abdomen and extremities, while 23% of histiocytomas occur at osseous sites. Although they can be found in the head and neck region, their occurrence is uncommon, accounting for 3%-8.5% of the cases [16-19]. In the head and neck, the nasal cavity and the paranasal sinuses are the most commonly affected sites and subsequently, the maxillary alveolar bone is often affected [19]. Mandibular MFH accounts for only 3% of all MFH bone lesions [20]. The peak occurrence is in persons aged 50-70 years. A slight male predominance is observed. They can occur everywhere, owing to

Patient	Age	Treatment	Follow-up post-therapy (mo)	Status at last follow-up	PTEN immuno-staining
1	38	S+R+C	26	AWD	+++
2	66	S	11	R	+
3	58	S+R	52	AWD	-
4	69	S	4	R.DOD	-
5	72	S+C	31	R	-
6	50	S+R+C	26	AWD	+++
7	61	S+R	6	R	-
8	62	S	12	R	-
9	70	S+R	33	AWD	-
10	68	S	12	R	-
11	71	S	18	R	-
12	57	S+R	29	AWD	+++
13	78	S+R	11	R	-
14	63	S+C	13	AWD	+++
15	59	S+R	35	AWD	+++
16	61	S	11	R	+
17	65	S	9	R	-
18	56	S+R	23	AWD	+++
19	39	S+R+C	18	AWD	+++
20	49	S+R	13	AWD	-
21	70	S	8	R	+
22	63	S	7	R	+
23	54	S+R	5	R	-
24	66	S	6	R.DOD	-
25	64	S	3	R	-
26	62	S+C	6	R	-
27	46	S+R+C	21	AWD	+++
28	55	S+R	19	AWD	-
29	53	S+R	24	AWD	+++
30	62	S	7	R	-
31	42	S+R	9	R	-
32	70	S+C	20	AWD	+++

S=Surgery; R=Radiotherapy; C=Chemotherapy
AWD: Alive with Disease; DOD: Dead of Disease; R: Recurrence

Table 2: Relationship between the immuno-staining of the primary tumor for PTEN and the outcome of 32 patients of MFH.

PTEN immune-staining	No. of cases	Response		
		Non	Partial	Complete
Negative	12	8	4	0
Positive	8	0	0	8

Table 3: Relationship between PTEN immuno-staining and response to salvage chemotherapy in 20 patients with recurrent tumor.

their mesenchymal origin [21,22]. These findings were in accordance with our results. In contrast to the findings of this work, a slight male predominance is observed [21,22].

The treatment of choice for the oral and maxillofacial MFH is extended surgical resection provided that adequate margins of normal surrounding tissues can be obtained [23]. Wide resection with clear margins is very important for improving survival [24]. But it is often difficult to conduct extended resection of a head and neck lesion with a wide margin of safety. Therefore, the treatment for head and neck MFH results in a significantly adverse outcome when compared with the treatment for MFH arising in other regions. Thus, many researchers have reported that a combination of radical excision, radiotherapy, and chemotherapy for head and neck region MFH was more effective [16,24,25].

Recurrence is related to size, depth of invasion, and microscopically positive surgical margins [26]. The proportion of the local recurrence rate of MFH after initial local excision ranges between 16% and 52% [27,28]. Yamaguchi et al. [24] revealed however local recurrence was less common in patients with adjuvant therapy (radiation therapy and/or chemotherapy) comparing with patients treated by surgery alone [24]. Nevertheless, another study revealed that the overall survival rate in patients with adjuvant therapy was lower than patients treated by surgery alone [24]. These results were in agreement with our result.

MFH has been divided into 5 subclasses: storiform-pleomorphic type, myxoid type, giant cell type, angiomatoid and inflammatory type [23,29]. The findings of the present studied cases showed that the major MFH variants belong to the storiform-pleomorphic type. Ozzelo et al. [30] and O'Brien et al. [21] stated that storiform-pleomorphic type is the most common type, and is a highly cellular tumor, which can range from well differentiated to anaplastic. While Ogura et al. [31] divided MFH into 4 categories: storiform predominance, myxoid predominance, inflammatory predominance, and pleomorphic. This classification may be of some significance with respect to prognosis;

the storiform and myxoid patterns are associated with a good prognosis because they metastasize slowly and respond well to surgical therapy. The inflammatory, and to a lesser degree, the pleomorphic variants, are more aggressive, they metastasize early, and respond less favorably to surgery alone.

Oral and jaw bone tumors are more aggressive than the tumors of the other sites of head and neck. However, the identification of a subgroup of less aggressive tumors is difficult because of the limited number of accepted prognostic factors. The prognosis of MFH lesions is influenced by the depth of tumor infiltration into the surrounding tissues, the mass of the tumor, and the anatomic location of the tumor [32]. MFH is known to be resistant to most chemotherapeutic regimens [14,33].

PTEN is a recently identified tumor suppressor gene [1,34] that plays important roles not only in suppressing cancer but also in regulating apoptosis [35,36]. Loss of PTEN expression has been detected in many cancers, including those of the human brain, breast, prostate, and lymphoid cells [34,37-39].

In this study, eight cases of storiform- predominance MFH demonstrated a positive immune reaction to PTEN in contrast to the negative reaction was noted in cases of both storiform-pleomorphic and inflammatory types of MFH. These results are in agreement with Pezziet et al. [28] who reported the more cellular tumors including the classic storiform-pleomorphic type make up the high-grade group and are highly aggressive [28,40,41]. In giant cell type of MFH, only four cases of the eight showed PTEN immunoreactivity in less than 50% of cells but the staining was of strong intensity. This finding may suggest that this subtype is an intermediate grade of malignancy. Moreover, PTEN positive expression in eight cases of storiform-predominance might reflect a better degree of differentiation and may represent an intrinsic prognostic factor in MFH.

The PTEN protein is a lipid phosphatase with putative tumor-suppressing abilities, including inhibition of the PI3K/Akt signaling pathway. Inactivating mutations or deletions of the PTEN gene, which result in hyperactivation of the PI3K/Akt signaling pathway, are increasingly being reported in human malignancies, including breast cancer, and have been related to features of poor prognosis and resistance to chemotherapy and hormone therapy [42]. These findings were in agreement with our results in which nearly almost MFH examined cases that showed loss of PTEN expression were resistant to chemotherapy and showed recurrence. While PTEN positive expression was associated with a better prognosis in MFH. These findings were in accordance with Ogura et al. [31] who found that the storiform and myxoid patterns are associated with a good prognosis because they metastasize slowly. The inflammatory, and to a lesser degree, the pleomorphic variants, are more aggressive, they metastasize early. However, statistically, no relationship was observed with the tumor size, histological subtype, or necrosis in our study.

Accordingly, the present study showed that both inflammatory and pleomorphic variants are a more aggressive and lower grade of malignancy than both storiform variant and giant cell type MFH. This is explained by the higher expression of PTEN in storiform variant than both pleomorphic and inflammatory types of MFH. Thus, loss of PTEN may serve as a reliable biological marker of high malignancy potential in MFH of the jaws. Furthermore, our interesting results supported that PTEN is the point of convergence of multiple signaling pathways and is involved in multiple antitumor effects such as anti-invasion, anti-proliferation, and anti-metastasis. Therefore, our future studies will focus on clarifying the intermediate steps that result in the ultimate effects and elucidate the relationship among various signaling pathways.

Conclusion

In conclusion, the present study has demonstrated that loss of PTEN may serve as a reliable biological marker of high malignancy potential in MFH of the jaws. Additionally, PTEN represents an important prognostic factor in MFH and is independent of tumor size; histological subtype, and necrosis. Moreover, loss of PTEN is an important event in regulating sensitivity to chemotherapy and is required for the development of resistance to chemotherapy in MFH cases. Thus, our results suggest that the PTEN gene may be a therapeutic target for treatment of MFH cases of the jaws.

References

1. Steck PA, Pershouse MA, Jasser SA, Yung, WA, Lin H, et al. (1997) Identification of a candidate tumor suppressor gene, MMAC1, at Chromosome 10q23.3 That is mutated in multiple advanced cancers. Nat Genet 15: 356-362.
2. Chu EC, Tarnawski AS (2004) PTEN-regulatory functions in tumor suppression and cell biology. Med Sci Monit 10: 235-241.
3. Whang YE, Wu X, Suzuki H, Reiter RE, Tran C, et al. (1998) Inactivation of the tumor suppressor pten/mmac1 in advanced human prostate cancer through loss of expression. Proc Natl Acad Sci USA 95: 5246-5250.
4. Rasheed BK, Stenzel TT, McLendon RE, Parsons R, Friedman AH, et al. (1997) PTEN gene mutations are seen in high-grade but not in low-grade gliomas. Cancer Res 57: 4187-4190.
5. Risingner JI, Hayes K, Maxwell GL, Carney ME, Dodge RK, et al. (1998) PTEN mutation on endometrial cancers is associated with favorable clinical and pathologic characteristics. Clin Cancer Res 4: 3005-3010.
6. Tanaka M, Koul D, Davies MA, Liebert M, Steck PA, et al. (2000) MMAC1/PTEN inhibits cell growth andinduces chemosensitivity to doxorubicin in human bladder cancer cells. Oncogene 19: 5406-5412.
7. Bates RC, Edwards NS, Burns GF, Fisher DE, et al. (2001) A CD44 Survival pathway triggers chemoresistance via lympho-kinase and phosphoinositide 3-kinase/akt in colon carcinoma cells. Cancer Res 61: 5275-5283.
8. Page C, Lin HJ, Jin Y, Castle VP, Nunez G, et al. (2000) Overexpression of Akt/AKT can modulate chemotherapy-induced apoptosis. Anticancer Res 20: 407-416.
9. Oda Y, Tamiya S, Oshiro Y, Hachitanda Y, Kinukawa N, et al. (2002) Reassessment and clinicopathological prognostic factors of malignant fibrous histiocytoma of soft parts. Pathol Int 52: 595-606.
10. Ahlen J, Weng WW, Brosjo O, Von Rosen A, Larsson O, et al. (2003) Evaluation of immunohistochemical parameters as prognostic markers in malignant fibrous histiocytoma. Oncol Rep 10: 1641-1645.
11. Mandard AM, Petiot JF, Marnay J, Mandard JC, Chasle J, et al. (1989) Prognostic factors in soft tissue sarcomas amultivariate analysis of 109 cases. Cancer 63: 1437-1451.
12. Costa J, Wesley RA, Glatstein E, Rosenberg SA (1984) The grading of soft-tissue sarcoma. results of a clinical pathologic correlation in a series of 163 cases. Cancer 53: 530-541.
13. Kulander BG, Polissar L, Yang CY, Woods JS (1989) Grading of soft tissue sarcomas: Necrosis as a determinant of survival. Mod Pathol 2: 205-208.
14. Enzinger FM, Weiss SW (1988) In: Louis S (ed.) Soft tissue tumors. Mo: Mosby-Year Book.
15. Riggs CE, Bennett JP (1991) Principles of cancer chemotherapy. In: Moossa AR, Schimpff SC, Robson MC (eds.) Comprehensive textbook of oncology. Williams and Wilkins 1: 527-528.
16. Young YH, Hsieh T (1989) Malignant fibrous histiocytoma of the head and neck: Report of 5 Cases. J Formosan Med Assoc 88: 606-609.
17. lin hs, sidhu g, wieczorek rl, galli srd, kaufman d (2001) malignant fibrous histiocytoma arising in the upper posterior triangle of the neck. Ear Nose Throat J 80: 560-567.

18. Sima AA, Ross RT, Hoag G, Rozdilsky B, Diocee M (1986) Malignant fibrous histiocytomas. histologic, ultrastructural and immunohistochemical studies of two cases. Can J Neurol Sci 13: 138-145.

19. Sato T, Kawabata Y, Morita Y, Noikura T, Mukai H, et al. (2001) Radiographic evaluation of malignant fibrous histiocytoma affecting maxillary alveolar bone: A report of 2 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 92: 116-123.

20. Kanazawa H, Watanabe T, Kasamatru A (2003) Primary Malignant fibrous histiocytoma of the mandible: Review of literature and report of a case. J Oral Maxillofac Surg 61: 1224-1227.

21. O'Brien JE, Stout AP (1964) Malignant fibrous xanthomas. Cancer 17: 1445-55.

22. Kempson RL, Kyriakos M (1972) Fibroxanthosarcoma of the soft tissues. A type of malignant fibrous histiocytoma. Cancer 29: 961-976.

23. Jamal BT, Tuluc M, Gold L, Heffelfinger R, Taub DI, et al. (2010) A radiolucent lesion in the posterior mandible. J Oral Maxillofac Surg 68: 1371-1376.

24. Yamaguchi S, Nagasawa H, Suzuki T, Fujii E, Iwaki H, et al. (2004) Sarcomas of the oral and maxillofacial region: A review of 32 cases in 25 years. Clin Oral Investig 8: 52-55.

25. Lin HS, Sidhu G, Wieczorek RL, Galli SRD, Kaufman D (2001) Malignant fibrous histiocytoma arising in the upper posterior triangle of the neck. Ear Nose Throat J 80: 560-567.

26. Rastogi S, Modi M, Dhawan V (2008) Malignant fibrous histiocytoma of the anterior maxilla. J Clin Diag Res 3: 892-898.

27. Le Doussal V, Coindre JM, Leroux A, Hacene K, Terrier P, et al. (1996) Prognostic factors for patients with localizec primary malignant fibrous histiocytoma. A multicenter study of 216 patients with multivariate anaylsis. Cancer 77: 1823-1830.

28. Pezzi ME, Rawling MS, Esgro JJ, Pollock RE, Romsdahl MM (1992) Prognostic factors in 227 patients with malignant fibrous histiocytoma. Cancer 69: 2098-2103.

29. Rapidis AD, Andressakis DD, Lagogiannis GA, Douzinas EE, et al. (2005) Malignant fibrous histiocytoma of the tongue: Review of the literature and report of a case. J Oral Maxillofac Surg 63: 546-550.

30. Ozzello L, Stout AP, Murray MR (1963) Cultural characteristics of malignant histiocytomasand fibrous xanthomas. Cancer 16: 331-343.

31. Ogura JH, Toomey JM, Setzen M, et al. (1980) Malignant fibrous histiocytoma of the head and neck. Laryngoscope 90: 1429-1440.

32. Barnes L, Kanbour A (1988) Malignant fibrous histiocytoma of the head and neck. A report of 12 cases. Arch Otolaryngol Head Neck Surg 114: 1149-1156.

33. Simon MA, Nachman (1986) The clinical utility of preoperative therapy for sarcomas. J Bone Joint Surg Am 68: 1458-1463.

34. Li J, Yen C, Liaw D, Podsypanina K, Bose S, et al. (1997) PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. Science 275: 1943-1947.

35. Di Cristofano A, Pandolfi PP (2000) The multiple roles of PTEN in tumor suppression. Cell 100: 387-390.

36. Huang H, Cheville JC, Pan Y, Roche, PC, Schmidt L, et al. (2001) PTEN induces chemosensitivity in PTEN-mutated prostate cancer cells by suppression of Bcl-2 expression. J Bio Chem 276: 38830-38836.

37. Depowski PL, Rosenthal SI, Ross JS (2001) Loss of expression of the PTEN gene protein product is associated with poor outcome in breast cancer. ModPathol 14: 672-676.

38. Hyun T, Yam A, Pece S, Xie X, Zhang J, et al. (2000) Loss of PTEN expression leading to high Akt activation in human multiple myelomas. Blood 96: 3560-3568.

39. Sakai A, Thieblemont C, Wellmann A, Jaffe ES, Raffeld M (1998) PTEN gene alteration in lymphoid neoplasms. Blood 92: 3410-3415.

40. Regezi JA, Zarbo RJ, Tomich CE, Lloyd RV, Courtney RM, et al. (1987) Immunoprofile of benign and malignant fibrohistiocytic tumor. J Oral Pathol 16: 260-265.

41. Fletcher CD, Gustafson P, Rydholm A, Willen H, Akerman M, et al. (2000) Clinicopathologic Re-evaluation of 100 malignant fibrous histocytomas: Prognostic relevance of sub-classification. J Clin Oncol 19: 3045-3050.

42. Garcia JM, Silva JM, Dominguez G, Gonzalez R, Navarro A, et al. (1999) Allelic loss of the PTEN region (10q23) in breast carcinomas of poor pathophenotype. Breast Cancer Res Treat 57: 237-243.