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Spectrum of Perivascular Tumors in a Teaching Hospital: An Indian Study of 16 Consecutive Patients in 5 years

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Abstract

Introduction: Separation of perivascular neoplasms from the "waste basket" category of hemangiopericytomas has obviated a need for more detailed look at this newly formed category of neoplasms.The lesions now remaining in perivascular tumor category are ones showing evidence of differentiation towards myoid / contractile perivascular cell and all share a characteristic tendency to grow in a circumferential perivascular fashion. *Aims:* To delineate the morphological features that characterise perivascular tumors and outline the morphological features seen in them. *Methods and Materials:* Perivascular tumors diagnosed in our institution over a period of five years were collected, we utilised H&E stained glass slides along with special stains to characterise and delineate the perivascular tumors. *Results:* 16 cases of perivascular tumors included 1case of glomus tumor, two cases of myopericytoma and thirteencases of myofibroma. One myopericytoma was of classical type while the other was an angioleiomyoma - like myopericytoma. 13 myofibromas could be sub classified into leiomyoma - like, vascular, nodular and multinodular type. *Conclusions:* Common features highlighted in the study indicate that perivascular tumors are part of a morphologic continuum, with categories defined by researchers being arbitrary. It would be suitable to merge them into a single entity, thus paving the way for use of the term hemangiopericytoma to denote all perivascular tumors, but only after morphological parameters for the usage of the term are clearly defined.

Keywords: Hemangiopericytoma; Myofibroma; Myopericytoma; Glomus Tumor; Angioleiomyoma.

Introduction

Separation of perivascular neoplasms from the "waste basket" category of hemangiopericytomas has obviated a need for more detailed look at this newly formed category of neoplasms.The lesions now remaining in perivascular tumor category are ones showing evidence of differentiation towards myoid / contractile perivascular cell and all share a characteristic tendency to grow in a circumferential perivascular fashion [1,2,3].

Today perivascular tumors consist of glomus tumor, myopericytoma, myofibroma, angioleiomyoma and so-called infantile haemangiopericytoma. We explore the spectrum of perivascular tumors to delineate the morphological features that characterise perivascular tumors and outline the morphological features seen in them.

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Methods and Materials

The material for present study comprised perivascular tumors diagnosed in our institution from January 2008 to April 2013. Clinical history and findings were recorded from the available requisition forms/ case records.

Specimens were fixed in 10% formalin for 6 to 48 hours. Large specimens were cut serially at distance of 1 cm before fixing in formalin. External appearances and cut sections were described. After fixation representative areas were sampled for detailed histopathological examination. Slides were stained

with hematoxylin and eosin stain. Microscopic findings were noted in a detailed manner in a proforma. Special stains (reticulin stain, Masson's trichrome stain) were performed wherever needed.

Results

Single case of glomus tumor in this study was a lesion measuring 0.75 cm in its greatest dimension, presented in the subungual region of right ring finger. Histologically tumor showed well circumscribed lesion with vessels in hemangiopericytoma like pattern and several layers of glomus cells also organized in nests. Stroma showed myxoid change at places. Glomus cells had rounded regular shape with round nuclei and moderate amount of eosinophilic cytoplasm (Figure 1). No atypia was noticeable.

Both myopericytomas in the present study were solitary lesions. Seen in a 68 years male and 14 years female, both had been present for a long time. Sclerosant therapy was given to lesion in the female, with a clinical diagnosis of cavernous hemangioma. The lesion showed no signs of regression 2 months after the injection, hence the lesion was excised. The lesion in the male measured 3 cm at its greatest dimension and was well circumscribed, grey white, solid lesion. The lesion in the female on the other hand was irregular, measuring 7 cm at its greatest diameter, grey white trabeculated appearance with two foci of haemorrhage within the lesion, probably demarcating the needle tracks of sclerosants. Lesions were unencapsulated, one was well circumscribed (Figure1B & 2A,B), both showed populations of monomorphic oval to spindle cells with myoid features showing concentric perivascular growth pattern. The cells had eosinophilic cytoplasm. Towards periphery blood vessels were more numerous, variable in size giving rise to a hemangiopericytoma like pattern.

Table 1: Clinical data: Perivascular tumors

Case No	Age (Yrs)	Sex	Location	Duration	Clinical Diagnosis	Histopath diagnosis
1	24	F	ring finger	6 Months	Dermoid	Glomus tumour
2	68	M	Lower limb	20 Years	Fibroma	Myopericytoma
3	14	F	gluteal Region	10 Years	Cavernous Hemangioma	Myopericytoma
4	55	M	Neck	NA	Lipoma	Myofibroma
5	28	M	Foot	3 years	Haemangioma	Myofibroma
6	28	M	Finger	NA	Ganglion	Myofibroma
7	78	M	Ankle	15 years	Sebaceous cyst	Myofibroma
8	50	M	Foot	5 years	NA	Myofibroma
9	27	M	Oral	4 years	Fibroma	Myofibroma
10	32	F	Finger	3years	Dermoid	Myofibroma
11	30	F	Multiple	Since birth	Fibroxanthoma	Myofibroma
12	22	F	Oral	NA	Fibroma	Myofibroma
13	55	F	Elbow	6 months	Soft tissue tumor	Myofibroma
14	45	M	Oropharynx	1 year	? Carcinoma	Myofibroma
15	50	M	Leg	2 years	Sebaceous cyst	Myofibroma
16	29	F	Leg	4 years	Ganglion	Myofibroma

Table 2: Morphologic features – Myofibroma

Sl. no	Size (cms)	Depth	Circumscription	Subtype
1.	1.5x1.5x1	Sub-cutaneous	Well	Leiomyoma
2.	2x1.5x1	Intradermal	Well	Leiomyoma
3.	7.5x3x1.5	Subcutaneous	Well	Leiomyoma
4.	1.5x1.1	Subcutaneous	Well	Nodular
5.	0.75x0.5x0.5	Subcutaneous	Well	Leiomyoma
6.	2x1.5x1	Submucosal	Well	Multi-nodular
7.	1.8x1x1	Subcutaneous	Well	Nodular
8.	6x4x2	Intra-dermal & Subcutaneous	Poor	Leiomyoma
9.	3x2x1.5	Submucosal	Well	Nodular
10.	2.5x2.1.5	Subcutaneous	Well	Vascular
11.	2x2x2	Submucosal	Well	Vascular
12.	1x1x1	Intra dermal	Well	Vascular
13.	1 cm	Intradermal	Well	Nodular

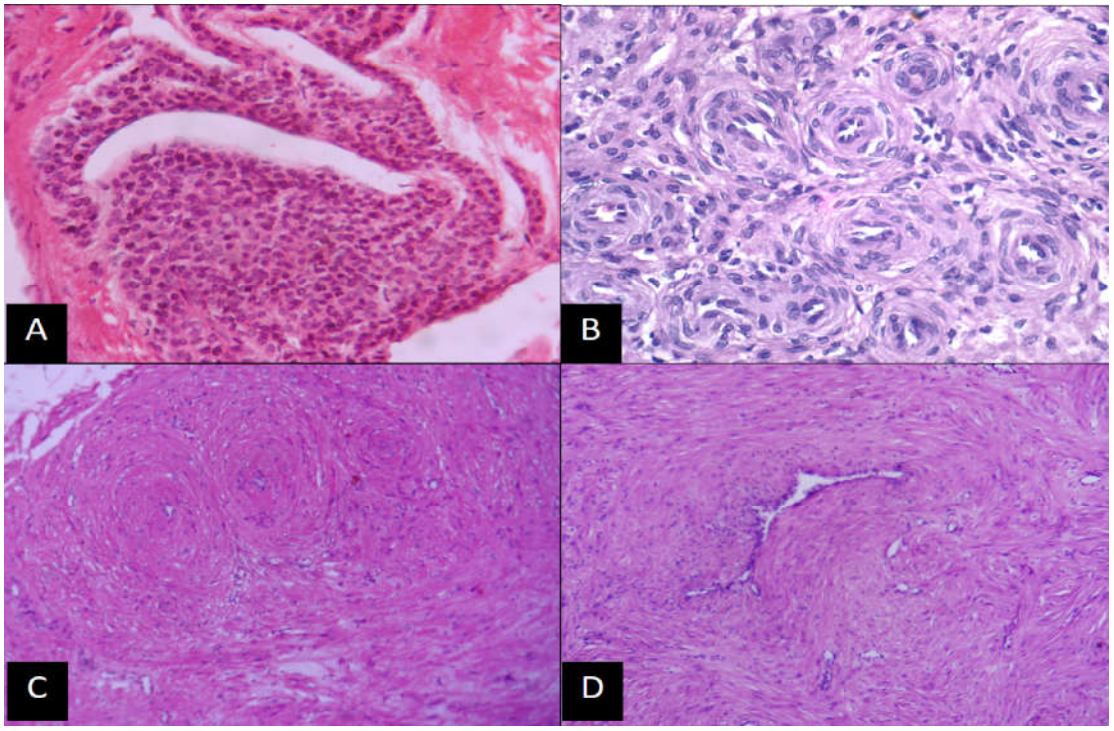

Fig. 1: A. Glomus tumor with perivascular plump glomus cells **B.** Myopericytoma with concentric arrangement of Myoid cells **C.** Nodular myofibroma with perivascular arrangement of Myoid cells **D.** Leiomyoma like Myofibroma with Hemangiopericytoma like vessels and vague perivascular arrangement of spindle cells.

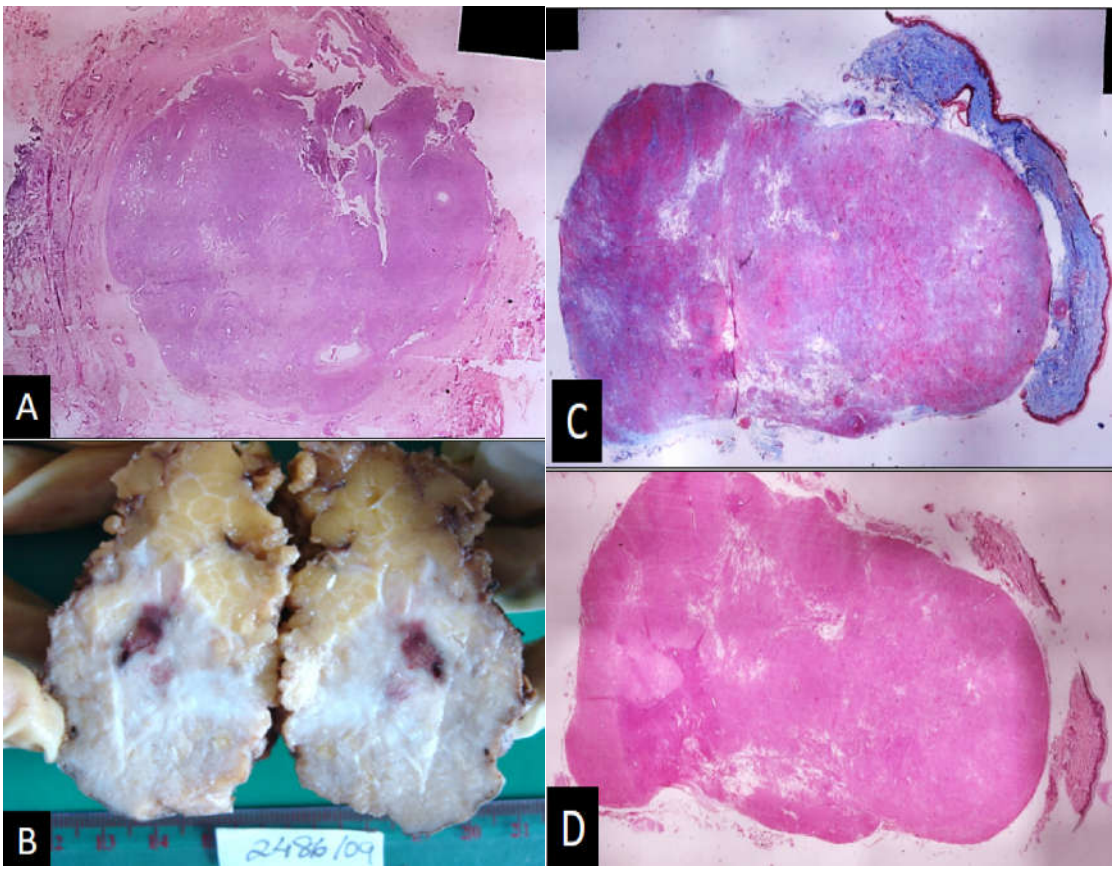

Fig. 2: A&B: Wholemount (H & E) and Gross in myopericytoma. **C & D**: Wholemount in myofibroma (Masson trichrome and H&E)

With regards to myofibroma, patients were mostly adults with ages ranging from 29-55 years. The lesions presented as solitary, usually painless nodules of variable duration on the skin, usually in the extremities. 3 cases were in oral and oropharyngeal area. In the patient with multiple subcutaneous nodules no visceral lesions were found, but similar swellings were noted in her sister also.

Histopathologically four patterns were identified: nodular or cellular type, multi-nodular or biphasic type, leiomyoma like or fascicular type and vascular type.

The nodular type lesion was sharply circumscribed with solid aggregations of plump spindle cells showing perivascular arrangement, but concentric perivascular pattern was only focally present. The cells had oval to elongate nuclei with abundant eosinophilic cytoplasm (Figure 1C, Figure 2C&D).

Multinodular or biphasic type consisted of multiple well circumscribed grouped nodules of spindle and plump cells in whorls but with more haphazard arrangement compared to infantile myofibromatosis.

The leiomyoma type showed poorly circumscribed fascicles of spindle cells with large pale eosinophilic cytoplasm and elongated tapering nucleus in haphazard arrangement (Figure 1D), intermingled areas of collagen were seen along with mucin.

The vascular type showed predominant vascular channels in haemangiopericytoma like pattern. Endothelial lining was present, pericyte like cells were seen in the walls. Thick collagen bundles were present at places.

Discussion

Perivascular tumors recapitulate the appearances of modified myoid cells that support or invest blood vessels. (i.e., glomus cell and pericyte) sometimes referred to as perivascular myoid tumors. Ever since the first description in 1942 by Stout and Murray of hemangiopericytoma as a tumor of pericytic origin, it has been a controversial entity. HPC–like pattern has been observed in many a neoplasm of diverse nature and hence HPC as a distinct neoplasm became a non–viable entity [2].

Today hemangiopericytoma as a distinct neoplasm is restricted only to hemangiopericytoma of sinonasal tract. Lesions now remaining in the category of perivascular tumors are glomus tumors, myopericytoma and myofibroma [2,4]

Hemangiopericytoma, while a distinctive lesion histologicaly, does not display true pericytic differentiation but shares many histologic, immunophenotypic and cytogenetic features with the solitary fibrous tumour. Because of the overlapping features of HPC and SFT and lack of clear criteria to determine if a lesion should be called SFT or HPC, pathologists have been gradually abandoning the term hemangiopericytoma in favour of the term solitary fibrous tumour [2,4,5].

The lesions remaining in pericytic / perivascular tumour category show evidence of differentiation towards myoid / contractile perivascular cells and all share a tendency to grow in circumferential perivascular fashion [6].

Eventhough divided into categories of glomus tumor, myopericytoma, myofibroma and angioleiomyoma based on predominant histologic pattern, this classification is artificial because these tumors comprise a histological continuum. Ultimately, this group of tumours may end up being renamed 'haemangiopericytoma' – but the latter can only happen once the loosely used understanding of haemangiopericytoma (which was a wastebasket diagnosis for many years) has been overcome [6,7].

Glomus tumours are subcategorised as solid glomus tumor, glomangioma, and glomangiomyoma depending on relative prominence of glomus cells, vascular structures and smooth muscle.Sites other than subungual location include arm, palm, legs, ankle, etc mostly in the extremities. Glomus tumours are rare soft tissue neoplasms. Even if only neoplasms of hand are considered, they constitute 1.5%, multiple lesions are seen in close to 10% of the patients [8].

In addition to deep dermis of distal extremities glomus tumours have been described in almost every location including mediastinum, penis, nerve, bone or viscera such as stomach, small bowel and lung. The lesion can be of long standing duration as has been shown in the studies compared herein [8,9,10]. The study of Granter et al [7] focused on glomangiopericytomas and looked for features to distinguish them from myofibroma and myopericytomas [7]. Single case of glomus tumor in our study was a well circumscribed lesion showing glomangioma like pattern, with HPC like arrangement of vessels lined by single to several layers of glomus cells. Concentric perivascular arrangement was absent.

Myopericytoma is described as an unusual tumor under hemangiopericytoma category, Granter et al suggested the name myopericytoma for the first time delineating these lesions from myofibromatosis of adults and glomangiopericytomas [7].

Perivascular tumors represent a histological

continuum including three arbitrary categories based on predominant histological pattern myofibromatosis, glomangiopericytoma and myopericytoma [7].

A predominant pattern of concentric proliferation of perivascular myoid cells is used to make a diagnosis of myopericytoma. Studies are still emerging which hope to morphologically and immunohistochemically differentiate between myopericytoma and other tumors which form its close differential diagnosis. The list includes angioleiomyoma and angiosarcoma besides the other perivascular tumors [7,11,12].

The age range is wide for myopericytomas, middle age being most commonly affected. Males predominate over females, extremities are more commonly involved. In their study, Mentzel et al [1] have recorded two cases with multiple lesions. They make no comment regarding duration of the lesions. Similar is the case with Granter et al [7] who had history of duration in only one of their seven cases. Dray et al [12] have recorded a median duration of 24 months in their study from 4 out of 7 cases of myopericytomas. Both our cases had a long history of 20 years and 10 years.

Granter et al [7] reported a tumor size ranging from 0.5 cm to 1.7 cm in their study. Largest tumor recorded by Mentzel et al [1] was 10.9 cm in the thigh. All lesions reported by Granter et al [7] were dermal or subcutaneous Mentzel et al [1] have, in their larger series, reported cases in the deep soft tissues and intravascular myopericytoma, however majority of the lesions were in dermis and / or subcutaneous plane. Multiple lesions have been described, but solitary lesions are encountered commonly.

Histologically, thin walled vessels and a concentric perivascular arrangement of ovoid, plump spindled to round myoid tumor cells were seen. A broad morphologic spectrum ranges from hypocellular fibroma like, myofibroma like, angioleiomyoma like and HPC like to classic myopericytomas. Going by this sub typing we observed one case which was a classical myopericytoma and another angioleiomyoma like myopericytoma.

Mentzel et al [1] described that the neoplasms that form differential diagnosis for myopericytoma that is myofibroma, glomus tumour and angioleiomyoma usually lack the characteristic perivascular concentric growth of myoid tumour cells, which is a salient feature of myopericytoma. HPC like pattern is less prominent in myofibroma, while the biphasic zonation pattern is more prominent. Cells in myopericytoma will show more glomoid features while in myofibroma the cells more closely resemble smooth muscle cells.[1,12]

Dray et al have [12] opined that because the myopericytoma like and glomangiopericytoma like patterns share so many features, they are best regarded as a single entity. This observation is in contrast to Granter and colleagues [7] who described myofibromatosis in adults, glomangiopericytoma and myopericytoma to be a spectrum.

Matsuyama et al [11] reviewed 130 cases of angioleiomyomas and found perivascular concentric growth atleast focally in 27 cases (20.8%), this interesting observation has led them to suggest that perivascular concentric growth alone may not be sufficient criteria to accurately call a lesion myopericytoma [11].

Describing infantile myofibromatosis as a distinctive clinicopathological entity in 1981, Chung and Enzinger made a brief mention that myofibromatosis occasionally occurs in adults. With case reports appearing in articles, cutaneous myofibroma and solitary myofibroma in adults have become accepted terms. Requena et al [13] proposed that cutaneous myofibroma in adults is a benign vascular neoplasm composed of immature pericytes or myopericytes after presenting their experience of 53 cases of cutaneous adult myofibroma [13].

The mean age in our study is 44.5 years which is comparable to other studies. Myofibromas are more common in males, as in our study. Only Requena et al [13] have found female predominance. We also found a predilection for distal parts of extremities in myofibromas as in other studies [3,12-14].

Myofibromas are benign, slow growing lesions which are painless in a majority of patients. The preoperative duration is not always reliable as it is not the time since the lesion appeared but the time since the patient noticed the lesion. Nevertheless, Requena et al [13] have observed a correlation between lesional age and histopathological pattern in their study.

Suggested clinical diagnoses in myofibromas were variable. Cutaneous dermatofibroma, cyst, lipomas and angioma being the most frequent clinical diagnosis.

Guitart et al [14] recorded maximal lesional dimensions of 0.6 to 1.5 cm. Median size of lesions is 2.5 cms. Myofibromas in dermis and subcutis are well circumscribed firm nodules which on cut surface have, firm, fibrous appearance with colours varying from grayish white, light tan to brown or purplish. Areas of necrosis may be evident at the center.

Requena et al [13] have described four histopathological variants of myofibroma : nodular or cellular type, multinodular or biphasic type,

leiomyoma like or type, and vascular type. A correlation was observed between the histopathological pattern and lesion age. Recently acquired lesions showed a vascular pattern with hemangiopericytoma like and glomus like areas, whereas older lesions showed nodular or multinodular cellular patterns, and late stage lesions exhibited leiomyoma like features with poorly cellular and hyalinised areas. Similar chronological sequence in the histopathological evolution of lesion of infantile myofibromatosis has been described [13].

In our study we could subclassify the myofibromas into four histopathological variants that have been described: nodular or cellular, multinodular or biphasic type, leiomyoma like or type and vascular type. A correlation has been observed between the histopathological pattern and lesion age. Recently acquired lesions show a vascular pattern with HPC and glomus like areas, whereas older lesions show nodular or multinodular cellular patterns and late stage lesions exhibit leiomyoma like features [13]. Duration was available in 10 of our cases and correlated with the chronological sequence that has been reported.

The cell of origin is still under debate. Based on ultra-structural characteristics neoplastic cells appear to be myofibroblastic in origin, which is intermediate between fibroblast and smooth muscle cells [12,13,15].

Histopthological differential diagnosis of myofibroma include dermatofibroma, NF, neurofibroma, neurothekeoma, leiomyoma, glomus tumor and myopericytoma.The absence of smooth muscle fascicles and cigar shaped nuclei helped rule out other smooth muscle tumors like fibroleiomyoma and angioleiomyoma that are positive for desmin and SMA. In a study of oral smooth muscle lesions, Masson trichrome stain has been shown to be useful. Overall, myofibromas were composed of much more collagenous stroma intermixed with the spindle cells and fibrous bundles with random, irregularly intersecting angles. Smooth muscle neoplasms showed only delicate fibrous tissue surrounding cells and in septa between masses. Authors however add that MTS can be used to assist in differentiating myofibromas from smooth muscle lesions but immunohisto-chemistry is still needed to rule out other spindle cell lesions [16].

NF which involves fascial plane, has a more prominent myxoid matrix, scattered chronic inflammatory cells and extravasated erythrocytes. Dermatofibroma, has a more pronounced storiform growth pattern, usually accompanied with epidermal hyperplasia, areas of focal lipidisation, giant cells and thick sclerotic collagen bundles surrounded by neoplastic cells at the periphery. It shows focal staining for SMA and is usually positive for factor XIIIa; finally neurofibroma is positive for S 100. It is worthwhile to note that all these tumors lack HPC like vascular pattern [12].

Myofibromas of the oral cavity have been reported rarely as sporadic case series or as small series.

As described by Vered et al [17] and Montgomery et al [18], most, if not all, previously reported cases of oral leiomyoma are more likely to be myofibromas. They express smooth muscle actin and are negative for desmin whereas leiomyomas express both the markers. This differentiation generally has little clinical significance, although myofibromas may be multifocal. However, these tumor foci are not true metastases [17,18,19].

Age of patients with myofibromatosis ranged from 23 to 67 years, with multicentricity in 4, local recurrence in 3, persistence of congenital lesions into adulthood in 4, and tumors that were multifocal within the confines of one anatomic region in 7 cases. Histologically, all showed a biphasic pattern that consisted of fascicles of spindle cells with abundant eosinophilic cytoplasm that resembled smooth muscle, in addition to a population of more primitive spindled cells associated with a HPC like vascular pattern. Six cases showed reversal of the typical zonation seen in pediatric cases in that the primitive component surrounded the more mature fascicular areas [07]. Multicentricity and positive family history in one case was not associated with reversal of zonation.

Conclusion

In the 2002 classification, the group of myopericytomas had been incorporated under this heading forthe first time (at the same time as haemangiopericytoma had been removed and listed as a synonym for solitary fibrous tumour). In the new WHO classification [20], it is acknowledged that myofibroma/myofibromatosis represent morphological points along the spectrum of myopericytic neoplasms, while the term 'myofibroma' can still prove to be useful in describing that subset of perivascular lesions which show predominantly myofibroblastic-like cytomorphology and prominent stromal hyalinization. Angioleiomyomas (vascular leiomyomas) have also been brought under the umbrella of perivascular tumors, as they also form a morphological continuum with the myoid end of the

spectrum of myopericytomas. Ultimately, this group of tumours may end up being renamed 'haemangiopericytoma'– but only after morphological parameters for the usage of the term are clearly defined.

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