Journal of Medical Sciences

ISSN 1682-4474

science alert

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Research Paper

J. Med. Sci., 11 (6): 250-255
15th August, 2011
DOI: 10.3923/jms.2011.250.255

Angulated Giant Cell with Clefting: A Clue to the Diagnostic Dilemma of Nodular Tenosynovitis

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Nodular Tenosynovitis (NTS) is a fairly common soft tissue lesion, often diagnosed as benign lesion clinically. Occasionally these, especially the recurrent lesions may mimic a malignant tumor, clinically and to a certain extent histologically. To highlight the characteristic morphological features especially of the angulated and 'kite shaped' giant cells with clefting and review the probable histiogenesis. Twenty one cases of NTS encountered in our centre over a period of 7 years including two recurrent lesions, closely mimicking melanoma and Malignant Fibrous Histiocytoma (MFH) were included in the study. Characteristic histological features with special attention to the morphology of the giant cells were observed and studied. These tumors are fairly easily recognisable histologically. The variable histomorphological features are described and those of diagnostic help highlighted, especially when one come across a highly cellular recurrent lesion mimicking malignancy. We have observed that giant cells are sparse in some tumors. When present, they are not the classical osteoclastic type, having fewer nuclei (average: 13). They have a peculiar angulated rather than smooth rounded border (64% angulated) with cleftin. (88% clefted). Awareness of the typical presentation, location and characteristic morphology should make the lesion easily recognizable. In a typical or recurrent lesions, a careful search for the sparsely distributed giant cell with a peculiar shape, presence of foamy histiocytes and iron demonstrable with a simple iron stain can resolve the dilemma, if any.

Key words: Nodular tenosynovitis, giant cell tumor of tendon sheath, angulated giant cell

JMS (ISSN 1682-4474) is an International, peer-reviewed scientific journal that publishes original article in experimental & clinical medicine and related disciplines such as molecular biology, biochemistry, genetics, biophysics, bio-and medical technology. JMS is issued eight times per year on paper and in electronic format.

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INTRODUCTION

Nodular Tenosynovitis (NTS) and Giant cell tumor of the tendon sheath are synonyms used to label a distinct subcutaneous nodular lesion mainly occurring in the distal extremities. Majority of these arise about tendons and joint spaces of fingers, toes, palm and foot (Enzinger and Weiss, 1995; Yoshida *et al*., 1974; Fleture and Horn, 1951). Despite having easily recognizable histological identity, they may be still overlooked by clinicians and pathologists and at times confused with a malignant lesion. We noted the presence of characteristic angulated giant cells with clefting in these lesions. This prompted us to review the cases diagnosed at our centre to identify helpful histomorphological features for diagnosis and review the theories of histiogenesis of this lesion.

MATERIALS AND METHODS

A retrospective study was performed. We could identify 21 surgical biopsies diagnosed as NTS at our Institute from Jan 2007 to June 2010. Clinical history and other relevant details were collected from the medical documents of the patient (Table 1). Formalin fixed paraffin embedded tissue samples were retrieved from the archives of The Department of Pathology. Haematoxilin and Eosin (H and E), other special stains and Immunohistochemical stains as required were performed. The slides were critically reviewed. The characteristic giant cells were analyzed based on number, shape, presence of clefting and the number of nuclei.

RESULTS

The average age of presentation was 42 years (Range 9-70 years) with male female ratio of 1: 1.1. The commonest complaint was a slowly growing painless nodular swelling on the distal extremities. Two were recurrent lesions. One recurrent lesion, recurring six months after excision, was ulcerated, indurated with irregular margins (case 10). All others were in the form of discrete, firm subcutaneous nodules attached to the underlying structures but free from the skin. The skin attachment could not be determined in one case where the nodule was on the fingertip with tight skin over it. No specific relation to joints or bones could be appreciated and none had complaints related to the joint mobility. One patient gave a history of trauma. Laboratory investigations like hemogram, ESR, rheumatoid factor, uric acid and serum calcium showed no abnormality.

The tumor size varied from 1 cm to the largest measuring 5×4×4 cm. Most were well circumscribed and vaguely lobulated. Cut surface had varied appearance-grey white, yellow to brownish with firm to soft consistency. The various clinical parameters of the 21 cases are listed in the Table 1.

Microscopically most of the tumors were moderately cellular showing sheets of spindle, polygonal and round cells with variable less cellular areas of fibrotic collagenised tissue (Fig. 1a). Foamy macrophages were variable but were invariably present in some parts of the tumor (Fig. 1b). Pigment laden macrophages and other inflammatory cells were also seen in variable proportions in all the cases (Fig. 1c).

Multinucleated giant cells were also highly variable. In fact, these were absent in some areas and sections, contrary to the impression implied by the term giant cell tumor of the tendon sheath. In some lesions, especially the highly cellular recurrences, very sparse giant cells were seen. These giant cells were not exactly simulating osteoclastic giant cells. They were smaller and often had less number of nuclei (Average: 13). Their cytoplasmic margin had peculiar angulated borders and sharp corners (paper kite head like or stretched diamond shape) (Fig. 2a). The giant cells invariably had a clear space bordering at least part of their cytoplasmic margin. Evaluation of the morphological features of giant cells is depicted in Table 2.

The one case, which needed to be highlighted was case 10, a 47 year old lady who had undergone surgery one year back for a lesion on the wrist. The lesion recurred six month later, enlarged, became painful and ulcerated. Detailed history of the original excision was not available. On examination she was found to have an ulcerated, indurated irregular mass with brownish black areas approximately 5 cm in diameter. The margin and base appeared irregular and infiltrating. Strong suspicion of melanoma was entertained and wide excision was attempted. Since it was difficult to remove en-masse, piecemeal thorough excision was done. (Total size 5×4×3 cm). Microsections of the growth showed highly cellular areas with monomorphic sheets of round cells having large vesicular nuclei, prominent nucleoli, high nucleo-cytoplasmic ratio and increased mitoses (Fig. 1d). Intracytoplasmic fine brownish black pigment granules were also seen, further contributing to the suspicion of melanoma. Possibility of high grade lymphoma was also considered. Multiple sections were studied. Clue to the diagnosis of NTS was the few collections of reactive foam cells and an occasional benign looking giant cell of the characteristic morphology

Table 1: Clinical details of 21 cases of NTS

Age	Sex	Site	Duration	Size	Histopathology	Clinical diagnosis
47	M	Left index finger	6 months	2×1×1 cm	NTS	Fibroma
9	M	LT palm	2 year	3×2×2 cm	NTS	PVNS
34	M	RT little finger	1 years 5 months.	2×1×1 cm	NTS	Fibroma
32	M	Little finger	3 year 2 months	2×1×1 cm	NTS	Ganglion
37	M	Knee	6 months	4×3×3 cm	PVNS	Giant cell tumor of tendon sheath
40	F	Knee	4 year	3×3×2 cm	NTS	Lipoma
40	M	Volar aspect of hand	2 year	2×2×1 cm	NTS	Lipoma
11	F	Lt thumb	3 year	2×1×1 cm	NTS	Neurofibroma
60	M	Knee	1 years	4×3×2 cm	PVNS	Ganglion
47	F	Wrist, recurrent lesion, ulcerated	6 months	5×4×4 cm	NTS	Melanoma
30	M	Foot, recurrent lesion	2 year	4×3×2 cm	NTS	Fibrosarcoma/MFH
65	M	Knee	6 months	5×5×4 cm	PVNS	Fibroma
11	F	Wrist	2 year	2×2×1 cm	NTS	Ganglion
60	F	Dorsal aspect of hand	2 year	2×2×1 cm	NTS	Lipoma
66	F	Wrist	6 months	3×2×2 cm	NTS	Ganglion
50	F	Ankle	2 year	2×2×1 cm	PVNS	Malignancy
23	F	Left leg	1 year	3×1×1 cm	NTS	Ganglion
28	M	Right wrist	6 months	2×1.3×1 cm	NTS	Ganglion
46	F	Left wrist	1 year	3×1.3×1 cm	NTS	Ganglion
60	F	Right thumb	1 year	1.5×2×1 cm	NTS	Tenosynovitis
61	F	Left wrist	2 years	2×1×0.3 cm	NTS	Ganglion

Table 2: Study of giant cells in NTS

			Shape of giant cells		Clefting around the giant cells		
Case No.	No of sections studied	Average no of giant cells in representative sections	Angulated	Round	Present	Absent	Average no of nuclei per giant cell
1	1	102	65	37	100	2	13
2	3	20	12	8	16	4	5
3	2	51	36	15	48	3	15
4	3	58	36	21	55	3	20
5	2	120	68	45	110	10	14
6	5	83	59	25	72	11	14
7	3	48	33	13	42	6	15
8	1	4	2	2	3	1	9
9	2	48	30	18	42	6	12
10	3	60	38	22	43	17	13
11	4	100	63	37	95	37	14
12	3	50	34	16	47	47	15
13	1	22	12	10	20	2	6
14	3	110	68	42	103	7	14
15	4	59	36	23	53	6	20
16	2	58	38	20	50	8	16
17	5	73	59	14	68	5	14
18	3	58	37	21	52	6	13
19	2	64	38	26	43	17	15
20	3	44	31	13	40	4	12
21	2	6	4	2	4	2	9

seen in some sections (Fig. 2b). Prussian blue stain highlighted the pigment even in the malignant appearing cells. Masons Fontana and immuno histochemical markers for melanocytes and lymphoid cells were negative. The patient was followed up for one year and there was no recurrence.

The other case of recurrence (case 11) was a 30 year old male who had an excision of a mass on the dorsum of the foot 5 years back. Recurrence occurred 2 years later. Skin was not ulcerated. The re-excised tissue was diagnosed as malignant, probably MFH at another centre. On review at our centre by a soft tissue pathologist, it was diagnosed as NTS by noticing characteristic giant cells (Sparse) and other components in some areas of the tumor. He has no recurrence after 2 years of follow up.

DISCUSSION

Nodular Tenosynovitis (NTS) arise about tendons and joint spaces of fingers, toes, palm and foot (Enzinger and Weiss, 1995; Yoshida *et al*., 1974; Fleture and Horn, 1951). Pigmented Villonodular Synovitis (PVNS) tend to be larger, more diffuse and more clearly related to the synovium of larger joints like knee and ankle (Abdul-Karim *et al*., 1992). Degenerative changes in joints are more with PVNS. Both have similar constituents like

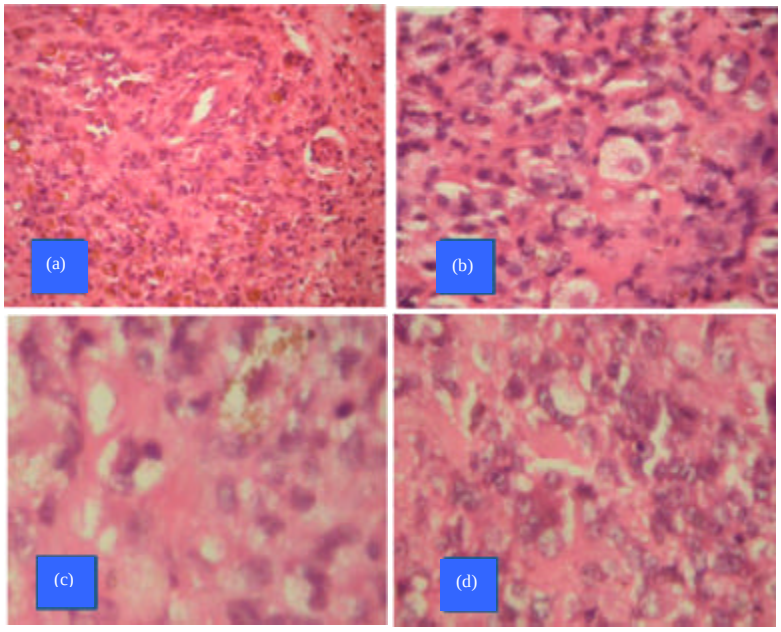

Fig. 1(a-d): (a) Round to polygonal cells blending in hypocellular collagenized stroma; (b) Foam Cells; (c) Pigment laden macrophage and (d) Pleomorphic tumor cells showing macronucleoli (H and E, x400)

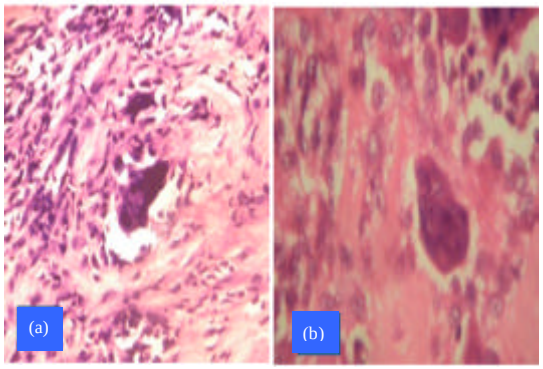

Fig. 2(a-b): Angulated giant cell with clefting (H and E, x400)

round or polyhedral histiocyte like cells, spindle cells, osteoclast like giant cells, foam cells and pigment laden phagocytic cells. Villonodular fonds of synovial proliferation are peculiar to PVNS (Schajowicz, 1981). However, NTS and PVNS may be manifestations of the same disease as suggested by Jaffe and associates (Lichtenstein and Sutro, 1941). But the usual absence of the obvious joint involvement and much more varied histological pattern mimicking other soft tissue or malignant tumors make NTS peculiar. It is often unsuspected by the surgeon and is likely to be misinterpreted by the pathologist as malignant, especially in the recurrent lesions with high cellularity and increased mitoses. We came across two such recurrent lesions where malignancy was suspected clinically and to some extent histomorphologically.

The main cellular components of this lesion are round or polygonal histiocyte like cells and fibroblasts, along with variable proportions of multinucleate giant cells, foam cells and hemosiderin laden macrophages. Slit like spaces also may be obvious. Unlike PVNS, NTS has no obvious relation to joint or synovium. A synovial related tumefaction is often not suspected clinically. Ushijima *et al.* (1986) have commented that the tumors arising in the digits are usually small, have a fibrous capsule, smaller number of cleft like spaces, sparse inflammatory infiltrate and thicker bundles of collagenous tissue as compared to PVNS which are larger, more diffuse, numerous cleft like spaces, villi covered by one or more layers of synovial cells, less collagenous tissue and moderate inflammation (Ushijima *et al.*, 1986).

We noticed that the giant cells in NTS has a morphologic feature which may help in identifying these lesions. These giant cells were not exactly simulating the osteoclastic giant cells in other giant cell lesions. These had lesser number of nuclei as compared to osteoclastic giant cells. We also noted that they had peculiar angulated border. Most of the giant cells were bordering

small cleft like spaces. Average number of giant cells in sections were 60 even as some sections had sparse no of demonstrable giant cells. Giant cells with angulated borders were 64% and those associated with clefts were 88%. The average number of nuclei in these giant cells were 13.

Two of our patients had recurrent lesions with high cellularity as noted by others (Roodrigues *et al*., 1988). One of them with ulceration, fixity, induration and apparent infiltration clinically mimicked melanoma. Histology as described earlier further nurtured the suspicion of melanoma or high grade lymphoma. However, the peculiar type of giant cells, foamy histiocytes and collagen bands seen in some sections appeared familiar to the picture seen in another recurrent NTS seen in the recent past. This prompted us to do an iron stain to identify the true nature of the malignant appearing round cells. Lymphocyte and melanocyte markers were also negative.

The identity of NTS, whether it is a true neoplasm or a reactive tumor like lesion is a matter of debate. The pathogenesis and histogenesis are also uncertain. Pathogenetic theories have included trauma, disturbed lipid metabolism, osteoblastic proliferation, infection, inflammation, vascular disturbances, immune mechanisms, metabolic disturbances and neoplastic process. Probably the most accepted theory is the one proposed by Lichtenstein and Sutro (1941) that it is a reactive or regenerative hyperplasia associated with an inflammatory process (Lichtenstein and Sutro, 1941).

Histochemical evidence suggests that the mononuclear cells and giant cells present in these lesions resemble osteoclasts of monocyte/macrophage lineage (Darling *et al*., 1997). PCR assays point to polyclonal nature of these cells and hence are probably non neoplastic (Vogrincic *et al*., 1997). Postulations are that these histiocyte like cells arise from synovial type A or fibroblast like type B cells. Actively proliferating histiocyte like cells, foam cells and presence of intracytoplasmic hemosiderin with obvious phagocytic attributes give credence to the histiocytic origin of this lesion (Schajowicz, 1981; Lichtenstein and Sutro, 1941; Ushijima *et al*., 1986). Eisenstein (1968) with ultrastructural studies, concluded that the basic cell types are the fibroblast like (B cell) and macrophage-histiocyte like (A cell) normally demonstrable in the synovium, as favored by the work of Ushijima *et al.* (1986) and Eisenstein (1968). Carstens (1978) after electron microscopic study of the tumor cells opined that the various types of cells in NTS are closely related to osteoblastic mesenchyme (Carstens, 1978). Cin *et al.* (1994) have brought out that, though these lesions have morphological uniformity, they are heterogenous by cytogenetic studies with chromosomal changes clustering in two regions 1p11 and 16q24 (Cin *et al*., 1994).

Local complete excision is the treatment of choice. Local recurrences as in two of our cases are probably due to the incompleteness of first excision.

To conclude, this study highlights angulated giant cells with clefting having lesser number of nuclei as compared to osteoclastic giant cell as a significant morphological finding of NTS. Variability exists in the appearance of cellular components and their distribution in different situations, different tumors and sections. Awareness about these variations and high cellularity in some lesions, a careful search for the characteristic giant cells and at times a simple iron stain will help in avoiding misinterpretation.

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