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Mast Cell Profile in Peripheral Nerve Tumours

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Abstract
Background*: Mast cells with a battery of crucial chemical mediators in their typical metachromatic granules are known to play a role in health and various disease states in man. This study was undertaken to evaluate the mast cell profile in peripheral nerve tumors.*
Materials & Methods*: The present study was carried out in the Department of Pathology, M R medical college, Gulbarga in all newly diagnosed peripheral nerve cell tumors.*
Sections were stained with H&E and 1% aqueous toluidine blue (pH=4) for mast cells. The mast cell count was performed per 10 HPF, tabulated, analyzed and statistically evaluated.
Results*: Significant increase (P < 0.05) of mast cells was observed in neurofibromas compared to schwannomas and MPNST. In schwannomas, Antoni type 'B' schwannomas showed a significantly higher (P<0.05) mast cell counts than the type 'A' schwannomas . Significantly higher (P < 0.05) mast cell counts were observed in schwnnomas compared to MPNST.*
Conclusion*: The study documented mast cell alteration in peripheral nerve tumors. These can be used as additional diagnostic parameter to differentiate between benign and malignant peripheral nerve tumors.*
Key Words*: Mast cells;*

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I. Introduction

The mast cells are invariably present in all organs of the human body and play a vital role in various inflammatory and immunopathological reactions, often linking the humoral and cell mediated phases of processes. They are easily identifiable due to their metachromatic granules which are present in the cytoplasm, when stained with toluidine blue, cresyl violet, azure A and methylene blue.

Mast cells are normal constituents of peripheral nerve in humans and may be seen in both endoneurial and epineurial locations (Gamble and Goldby, 1961). Only occasional mast cells are seen in normal peripheral nerve (Nepriakhin, 1956). There is a definite increase in mast cells in degenerations of nerves like wallarian degeneration (Rosenheim, 1886). Disorders of peripheral nerves most notably Von Recklinghausen neurofibromatosis are associated with increase in mast cells, (Olsson, 1971). Precise role played by mast cells in peripheral nerves is intriguing. Tumors of peripheral nerves form a remarkable and complex subject regarding their histogenesis, classification and their diagnosis. Few scientists have described alterations in mast cell distribution in various benign and malignant nerve tumours. (Mahion D. Johnson,1989). Harkin and Reed, (1969) have commented that presence of mast cells in a spindle cell tumours suggests the diagnosis of Neurofibroma.

Considering this background the present study attempted to evaluate mast cell alterations in various peripheral nerve tumors; to look for any distinguishing criteria between neurofibromas and schwannomas and also for changes in benign versus malignant nerve sheath tumors.

II. Methodology

The present study was carried out in the department of Pathology, Mahadevappa Rampure Medical College, Gulbarga by carefully screening the slides of peripheral nerve tumours along with the relevant available clinical data.The study included 31 Schwannomas (14 cases of type 'A' Schwannomas, 9 cases of type 'B' Schwannomas and 8 cases of mixed Schwannomas), 14 cases of neurofibromas and 9 cases of malignant peripheral nerve sheath tumours.

The tissues for histopathological study was fixed in 10% buffered formalin, processed in different grades of alcohol and were embedded in paraffin. The sections were cut at 5 micron thickness and staining was done with haematoxylin and eosin and 1% aqueous toluidine blue.

Peripheral nerve tumors were categorized according to the following criteria (Harkin and Reed,

1968).
MAST CELL STAINING AND COUNTING:
To identify those mast cells with the typical metachromatic granules, special stain 1% aqueous toluidine blue at pH 4 was used.
Toluidine Blue Staining Method: (Clayden EC. 1962)

1) Preparation of staining solution: - 1gm of toluidne blue powder is dissolved in l00ml of distilled water .and the pH is adjusted to 4. The solution is filtered before use.
2) Staining Procedure :-
(a) The sections were taken on albuminised slides,deparaffinisation done, then brought to water and stained with toluidine blue for 1 min.
(b) Then the slides were rinsed in water, differentiated in 95%, alcohol, cleared in Xylene and mounted in D.P.X. mountant.
3) Results: — Mast cell granules – Purple
Surrounding tissue - Blue.
4) Mast cell counting and observation: - Toluidine blue stained sections were examined under high power magnification. The number of mast cells present in the 10 consecutive high power fields were counted in all the sections and tabulated. The results were statistically evaluated. The state of granularity of mast cells was also observed. The metachromasia of the connective tissue was recorded as absent, present (diffuse or patchy).
On the basis of observations an attempt was made to study distribution pattern of mast cells in relation to -
(1) Schwannomas and neurofibronias.
(2) In schwannomas between type 'A' and type 'B' areas.
(3) Benign versus malignant nerve sheath tumours.

III. Observations

The present study has been attempted to look for mast cell alterations in various peripheral nerve turnours. Thirty one schwannomas, fourteen neurofibromas, and nine malignant peripheral nerve sheath tumours(MPNST) were included in the study.

The age distribution of patients in neurofibromas ranged from 13 years to 54 years with a mean age of 31.78 years and a male to female ratio of 3:1.6 (Table-1). In schwannomas age of patients ranged from 23 years to 50 years with a mean age of 36.66 years and male to female ratio of 3:8 (Table-1). In MPNST age of patient ranged from 20 years to 58 years with a mean age of 39.11 years and male to female ratio of 2:1 (Table-1).

Sites: The usual sites of these peripheral nerve tumors were skin and subcutaneous tissues of extremities - mainly upper limbs. Other sites included chest wall and neck. Rare sites included abdominal cavity.

Gross: Size of benign neoplasms ranged from 1.5cms to 5cms in diameter and were grey white to white in colour with homogenous appearance on cut surface except for few which showed cystic degeneration. Malignant neoplasms (MPNST) were of 4cms to l2cms in diameter, irregular, friable, with areas of haemorrhage and necrosis.
SCHWANNOMAS: (31 cases)
Type 'A' Schwannomas : (14 cases) (Figure-6)

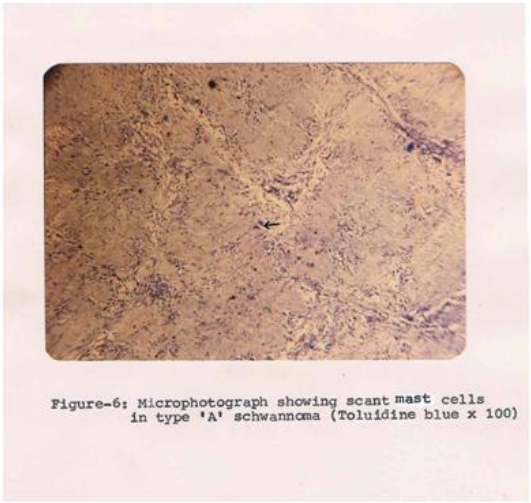

Figure-6: Microphotograph showing scant mast cells in type 'A' schwannoma (Toluidine blue x 100)

Mast cell distribution in type 'A' schwannomas most lesions showed increased concentrations of mast cells in subcapsular regions (7 cases) others showed no particular variations (6 cases) and only one case showed aggregation towards connective tissues septa. About 50% of cases showed connective tissue metachromasia of which some had diffuse pattern and others patchy distribution.

Type 'B' Schwannomas : (9 cases) (Figure-7)

Figure-7: Microphotograph exhibiting abundant mast cells in type 'B' schwannoma (Toluidine blue x 400)

Mast cell counts in these neoplasms with cystic change showed increased concentration of mast cells around the areas of cystic change (3 cases) , few cases showed aggregation of mast cells towards capsule and subcapsular regions (2 cases) with decreasing concentration towards centre. However, others showed diffuse pattern of distribution. Connective tissue rnetachromasia was present with patchy distribution in about 2/3rd of the cases.

On comparison and statistical analysis type 'B' Schwannomas showed increase ($P < 0.05$) in mast cell concentration versus type 'A' schwannomas. However, type 'B' schwannomas showed a definite decrease in mast cell counts compared to neurofibromas (mean value 18.50).

Mixed Schwannomas (8 Cases)

In mixed schwannomas mast cell there was no particular pattern of distribution of mast cells except that type 'B' tissue showed a definite increase in concentration of mast cells when compared to type 'A' tissue (P less than 0.05) (Table-2). Schwannomas as a whole compared to MPNST showed increase in mast cell counts ($P <0.05$) (Table-3). Patchy connective tissue metachrornasia was present in about 2/3rd of cases.

NEUROFIBROMAS : (14 cases) (Figure-8)

Mast cell counts in neurofibromas, there was no particular variation in distribution of mast cells except for one case which showed increased mast cells around the vicinity of blood vessels.

On analysis of statistical data neurofibromas showed definite increase ($P <0.05$) in mast cell counts as compared to schwannomas (Table-4). Statistical analysis also showed a definite increase in mast cell counts in neurofibromas compared to MPNST. ($P < 0.05$) (Table-5). Patchy connective tissue metachrornasia was present in half the cases of neurofibromas.

Malignant peripheral nerve sheath tumours (MPNST): (9 cases) (Figure- 9)

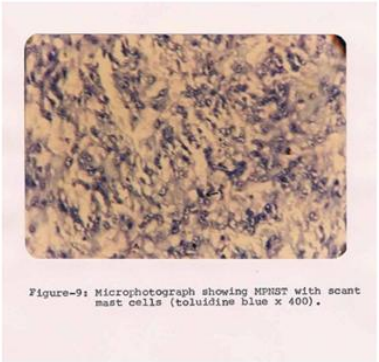

Figure-9: Microphotograph showing MPNST with scant mast cells (toluidine blue x 400).

Thesewas no particular pattern of distribution of mast cells which were widely scattered.
On comparison and statistical analysis of mast cell counts of schwannomas (Table-3) and neurofibromas (Table-4) with that of MPNST showed a significantly lower mast cell counts in MPNST. Connective tissue metachromasia was absent in most cases of MPNST.
Observations in the this study hightlight that there is a definite increase in mast cells in neurofibromas ($P < 0.05$) when compared to schwannomas. In the schwannomas, Antoni, type 'B' tissue showed more number of mast cells ($P < 0.05$) than Antoni type 'A' tissue.
However malignant nerve sheath tumours showed very low mast cell counts when compared to schwannomas and neurofibromas.
While connective tissue metachromasia was present in most benign tumours (Schwannomas and neurofibromas), it was strickingly absent in malignant peripheral nerve sheath tumours.

Table—1: Age and Sex distribution of peripheral nerve tumors

Tumour type	No. of cases	Age range	Average age	M:F ratio
Schwannoma	31	23—50 Yrs	36.66 Yrs	3:8
Neurofibroma	14	13—54 "	31.78 "	3:1.6
MPNST	9	20—58 "	39.11 "	2:1

Table—2: Mast cell pattern in various Schwannomas

Tumour type	**Mast cell count per 10 HPF**		**Statistical significance**
	Range	**Mean**	
Schwannoma type 'A'	2-14	5.14	$P < 0.05$
Schwannoma type 'B'	2-40	15.60	
Type 'A' area Mixed Schwannomas Type 'B' area	0-15 4-30	3.00 9.12	$P < 0.05$

Table—3: Mast cell distribution in Schwannomas versus MPNST

Tumour type	Mast cell count/10 HPF		Statistical Significance
	Range	Mean	
Schwannomas	0-40	10.29	$P < 0.05$
MPNST	0-6	1.80	

Table—4 Mast cell distribution in Schwannomas versus Neurofibromas

Tumour type	Mast cell count/10 HPF		Statistical Significance
	Range	Mean	
Schwannomas	0-40	10.29	$P < 0.05$
Neurofibroma	3-56	18.50	

Table-5 Mast cell distribution in Neurofibromas versus MPNST

Tumour type	Mast cell count/10 HPF		Statistical Significance
	Range	Mean	
Neurofibromas	3—56	18.50	$P < 0.05$
MPNST	0—6	1.80	

IV. Discussion

In the present study on mast cell profile is a preliminary approach to probe into the mast cell alterations in the peripheral nerve tumors.

Lot of work has been done on the presence of mast cell alterations in various tumours of man, (Bergonzini, 1891; Giani, 1964) and in various benign versus malignant neoplasms (Lascano, 1958. Various studies have tried to use the presence or absence of mast cells as a differentiating factor in various benign tumours, (Isaacson, 1971), as an indicator for presence or absence of malignancy, (F. Hartviet, 1981) or even to predict the histogenesis of tumours, (Mahlon D. Johnson, 1989). However, results of some studies lack a proper statistical correlation.

A carefull search of medical literature, revealed very few studies. However, studies done so far show consistent findings which correlated well with each other (Isaacson, 1971; Mahion D. Johnson, 1989).

The number of cases in the present study though not very large, appeared to be quite sufficient to draw logical conclusions which might prove to be of additional diagnostic or prognostic value.

On analysing and comparing the spectrum of mast cells in various peripheral nerve tumours in the present study, it is obvious that significantly increased ($P < 0.05$) mast cells were seen in neurofibromas (56/10 HPF). This finding correlates very well with that of Isaacson (1971) who documented a count of about 40-80 mast 'cells per 10 HPF in most neurofibromas and also suggested that these neoplasms could easily be distinguished from Schwannomas because of their mast cell content. This finding was further confirmed by Mahion D. Johnson who in 1989 also showed an increase in mast cell counts in neurofibromas.

In present study mast cell distribution in neurofibromas was relatively more even in majority of lesions, a finding which is emphasized in the study conducted by Mahion D. Johnson (1989). Mast cell counts in neurofibromas were significantly greater ($P < 0.05$) than those identified in Schwannomas and MPNST. It appears that mast cells represent a significant cellular component of neurofibromas which distinguishes it from other benign and malignant schwann cell neoplasm (Mahlon D. Johnson, 1989).

Mast cell response in relation to neoplasia appears to be an effect rather than a cause in pathobiology of tumours. It is of particular interest that mast cells in neurofibromas represent a dense reaction elicited by the tumour or they are a part of special inflammatory process characteristic of this disease, (Coronil and Michon, 1924).

Since limited number of mast cells are normally scattered within the epineurium, perineurium and endoneurium of normal nerve, their presence in neurofibromas is not surprising. However, the mast cell concentrations in neurofibrormas studied here in was significantly greater than that reported in nerves, suggesting active mast cell proliferation or infiltration into these nerve sheath tumours (Mahion D. Johnson, 1989).

Both experimentally in rat (Gamble and Goldby, 1961) and in man (Isaacson, 1971) mast cell proliferation in peripheral nerves occurs as a reaction to injury. It is endoneurial mast cells that proliferate accompanied by other nerve cells and tissues namely schwann cells, fibroblasts and collagen. Mast cells with their distinctive staining form a convenient label of reactive endoneurial tissue. Their presence in Antoni type 'B' tissue of Schwannomas can be explained by postulating a reaction to injury of the nerve by an expanding schwann cell neoplasm (Antoni type 'A' tissue), folds of reactive endoneurial tissue may become incorporated into the tumour as Antoni type 'B' tissue, (Isaacson, 1971).

Neurofibromas on the other hand because of their high mast cell content are thought to be reactive or hamartomatous lesions, support to this is found in ultrastructural studies of nerve sheath tumours (Waggener, 1966). Here it was shown that while Antoni type 'A' tissue of schwannomas contains almost entirely of schwann cells. Antoni type 'B' tissue and neurofibromas both consists of similar variety of elements including schwann cells, fibroblasts, histiocytes and collagen alongwith the mast cells. While schwannomas appear to push axons aside neurofibromas incorporate them suggesting a diffuse reactive process arising in perineurium.

Mast cells are involved in promoting growth of neurofibroma. Support to this is provided by studies conducted by V.M.Riccardi (1987) who noticed decrease in growth of neurofibromas and also decrease in symptoms like itching with ketotifen, a mast cell degranulation inhibitor. This finding was thought to reflect inhibition of growth factor release. However, inhibition of serotonin and histamine release, reducing vascular permeability and infiltration by suppresor macrophages and lymphocytes has also been shown to reduce tumour growth. Additional studies are required to elucidate the role of various factors like mast cells in oncobiology of neurofibromas.

In terms of diagnostic value of observations presented here, quantitation of mast cells facilitate differentiation of neurofibromas and schwannomas perhaps more accurately than immunohistochemical analysis. Previous attempts to differentiate these tumour types using antibodies that recognize S-100 protein; vimentin, Myelin basic protein, Myelin associated glycoprotein, (Leu 7), neurofilament, glial fibrillary acidic protein, epithelial membrane antigen, fibronectin and collagen types-I through IV have not identified highly diagnostic differences between neurofibronias and schwannornas (Stefanson K. Wollmann, 1982; Ariza A. Bilbao, 1988).

The present study of the mast cell spectrum in peripheral nerve tumours highlights that -

Mast cell response does occur in various peripheral nerve tumours. Highest mast cell concentrations were observed in neurofibromas. In schwannormas, Antoni type 'B' tissue had more concentrations of mast cells than Antoni type 'A' tissue. In MPNST mast cell counts were significantly lower than observed in neurofibromas and schwannomas.

A detailed in depth study of fascinating mast cells offers a wide scope for future research. Modulation of mast cells and their products by pharmacologic, immunologic or other means offers a favourable perspective in host tumour interactions, tumour biology and tumour therapeutics.

V. Summary And Conclusions

The present study - "Mast cell profile in peripheral nerve tumours" included 31 cases of schwannomas (14 type 'A' schwannomas, 9 cases of type 'B' schwannomas and 8 cases of mixed schwannomas), 14 cases of neurofibromas and 9 cases of MPNST.

Sections were stained with H & E Toluidine blue (PH4) staining was done for mast cells with typical metachromatic granules. The mast cell count was performed per 10 HPF, analysed and statistically evaluated and comparative analysis of mast cells in different peripheral nerve tumours was done.

In the present study of mast cell spectrum in peripheral nerve tumours highlights that -

(1) Mast cell response does occur in various peripheral nerve tumours.

(2) Variability of mast cell response is certainly observed in these tumours.
(3) Highest mast cell concentrations were observed in neurofibromas.
(4) In schwannomas Antoni type 'B' tissue had more mast cells than Antoni type 'A' tissue.
(5) In MPNST mast cell counts were significantly lower than observed in neurofibromas and schwannnomas.

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