Original Article

Mast Cell Association in Hemangiomas and Arteriovenous Vascular Malformations

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ABSTRACT

Background: Vascular anomalies, classified as hemangiomas and arteriovenous malformations (AVMs), were analyzed for the presence of mast cells. Hemangiomas in the proliferative phase contained large numbers of mast cells (53.12 ± 27.83 cells/mm2) in comparison with hemangiomas in the involuting phase (11.43 ± 7.9 cells/mm2), and AVM (25.31 ± 27.3 cells/mm2). Considering the fact that hemangiomas are characterized by endothelial proliferation and increased numbers of mast cells, these data raise the possibility that mast cells may have an important role in the formation and/or maintenance of these lesions.

Aim: This study aimed at evaluation of presence of mast cells in hemangiomas proliferating, involuting ones and AVMs.

Methods: A total of 120 cases of benign vascular lesions were retrieved from 12 years period. A total of 94 cases, where complete clinical details and representative paraffin sections were available, were included in this study. Hematoxylin and eosin (H and E) stain and Mast cell density in all lesions was calculated from toluidine blue stained sections.

Results: Mean mast cell density was significantly higher in proliferating hemangiomas (53.12 ± 27.83 cells/mm2) compared to involuting hemangiomas (11.43 ± 7.9 cells/mm2) and AVM (25.31 ± 27.3 cells/mm2)

Conclusions: The significantly higher mast cell density seen in proliferating hemangiomas compared with involuting ones, seem to suggest that mast cells play an important role in the natural history of these lesions.

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Introduction

Vascular anomalies comprise a widely heterogeneous group of tumors and malformations.[1] The diagnosis and management of these lesions present diagnostic and therapeutic challenges to surgeons, radiologists, and histopathologists. This is in part due to lack of agreement regarding the nosology and classification of these lesions both for diagnostic and therapeutic purposes.[2]

A history of rapid neonatal growth and slow involution, characterized by hypercellularity during the proliferating phase and fibrosis and diminished cellularity during the involuting phase were hemangiomas and those present at birth which grew commensurately with the child were characterized by a normal rate of endothelial cell turnover were arteriovenous malformations (AVM). Mulliken and Glowacki[4] believed that sophisticated laboratory techniques are not necessary to assign a lesion to either of the two major categories: Hemangioma or malformation. This classification was later accepted at the 1996 biennial meeting of the International Society for the Study of Vascular Anomalies.[5]

We studied mast cell density in hemangiomas and AVMs to determine if they differed significantly.

Materials and Methods

This study was carried out in the Department of Pathology, Mahatma Gandhi Institute of Medical Sciences, Sevagram, India from June 2006 to August 2008. The required funds for the study were self financed and no conflict of interest was confirmed. This study includes 120 consecutive cases of benign vascular lesions reported during a 12-year period (1997-2008). Complete demographic and clinical details of the patients including name, age, sex, clinical history, site of the lesion and histological diagnosis offered originally were retrieved from Surgical Pathology records. Cases where clinical details were incomplete, tissue blocks were unavailable or representative tissue was inadequate ($n = 26$) were excluded from the study group. Paraffin tissue blocks were retrieved in all the remaining 94 cases and these were included in the study. Sections were cut from each block containing the representative lesions and stained by 1.0% toluidine blue: To perform mast cell count. Mast cell counting was done in toluidine blue stained sections using Nikon YS100 model biological microscope in all the cases using 100 oil immersion objective and X 10 eye piece. With these specifications the magnification is X 1000 and field view diameter is 0.18 mm. Therefore, area of the field view using the formula for the area of a circle = $\pi r2$ (where r is the radius of a circle) is 0.0254 sq mm. Thus, for counting in 1 mm2 area, we have to do the cell count in 1/0.0254 = 39.37 fields, or rounded up to 40 fields. Therefore, 40 non-overlapping fields were counted to obtain mast cell count per mm^2 area. In each representative section, 40 fields were counted to obtain the number of cells per mm^2. All data were entered in MS Excel and statistical analysis was performed. Chi-square test was done using STATCALC calculator in EPI-INFO software (Version 6, Centres for Disease Control and Prevention, Atlanta, 1996).

Results

This study analyzes findings seen in 44 cases of AVM and 50 cases of hemangiomas, that is, in 94 cases of benign vascular lesions.

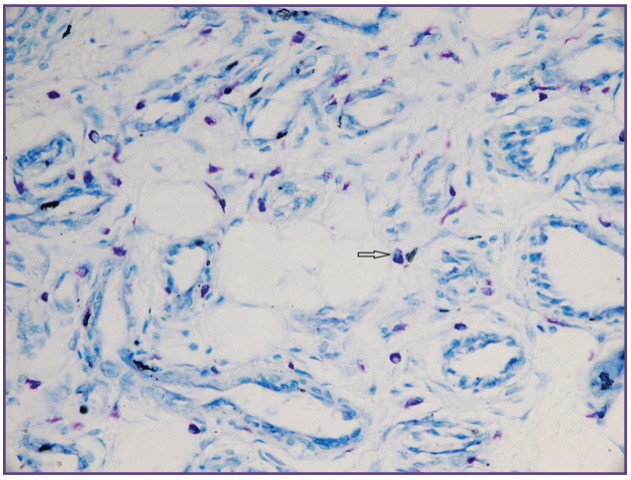

Fig. 1: Photomicrograph showing large number of mast cells in a case of proliferating hemangioma (Toluidine blue, ×1000). Mast cell-Arrow in the centre.

Table: Mean mast cell density in proliferating and involuting Hemangiomas

	Proliferating hemangiomas (n = 16)	Involuting hemangiomas (n = 23)
Range	6-136 cells/mm2	2-31 cells/mm2
Mean±SD	53.12±27.83 cells/mm2	11.43±7.9 cells/mm2

SD: Standard deviation

We found that the mast cell density ranged from 0 to 95 cells/ mm^2 in cases of AVM while it ranged from 2 to 136 cells/mm^2 in cases of hemangiomas. The mean mast cell density in AVM was 25.31 ± 27.3 cells/mm^2 while it was 29.36 ± 25.06 cells/mm^2 in hemangiomas and this difference was not statistically significant.

We compared mast cell density in involuting ($n = 23$) and proliferating ($n = 16$) hemangiomas. Only those cases, which showed clear cut evidence of proliferation or involution, were included in this analysis [Table]. Mean

mast cell density was significantly higher in proliferating hemangiomas [Figure] compared with involuting ones showing the presence of fibrosis (P= 0.028).

Discussion

Literature on the occurrence of the mast cells in benign vascular lesions is sparse and contradictory. This may be accounted for by the confusion in the classification and nomenclature of cutaneous vascular lesions. Burrows *et al*.[8] found a mean of 35.9 mast cells/high power field (HPF) in four hemangiomas, while the mean cell count in seven patients with vascular malformations was 0.7/HPF. Koutlas and Jessurun[7] found 6-22 mast cells/HPF in the stroma and around vascular components in 6 cases of AVMs. Girard *et al*.[6] also reported increased numbers of mast cells in the stroma, but they did not further elaborate on this observation. Carapeto *et al*.[9] mentioned the presence of mast cells around vessels. Lascano[10] and Baroni[11] identified increased numbers of mast cells in several vascular tumors. We compared the mast cell density in 16 cases of proliferating hemangiomas and 27 cases of involuting hemangiomas. The mean mast cell density in proliferating hemangiomas was 53.12 ± 27.83 cells/mm^2, while it was 11.43 ± 7.9 cells/mm^2 in involuting hemangiomas and arteriovenous malformations (25.31 ± 27.3 cells/mm^2). Mean mast cell density was significantly high in proliferating hemangiomas compared to involuting ones showing the presence of fibrosis. The wide range of values obtained from the mast cell counts proliferating hemangiomas (6-136 cells/mm^2) probably reflects the nature of these lesions, where there is the presence of dense proliferating nests of endothelial cells without capillary lumina at places to abundant capillaries at some places and to beginning of fibrosis and involution at others. In their study, Glowacki and Mulliken[12] found that the density of mast cells was at least five times more in proliferating hemangiomas of childhood than the density of mast cells of normal skin and that the mast cell numbers fell to normal in regressing tumors. Our data raises the possibility that the mast cells may have a role in formation, maintenance and progression of these lesions.

The striking feature of proliferating hemangioma in contrast to lesions in the involuting phase is hypercellularity with high labeling of endothelial cells by (3H) thymidine.[3] Azizkhan *et al*.[13] have shown that mast cell conditioned media stimulate the migration of microvascular endothelial cells *in vitro*. Heparin has been shown to be a potent stimulus of endothelial migration. Mast cells may enhance directional elongation of new capillary sprouts by sustained release of heparin. Heparin alone does not stimulate endothelial cell proliferation but is an important amplifier in angiogenesis. Hemangiomas thus may arise or be maintained by abnormal concentrations of mast cells within developing connective tissue; the endothelial cells and vascular channels may involute when stimuli from mast cells are no longer present. It is unlikely that mast cells alone are the direct cause of hemangiomas, yet their abundance in proliferative lesions only suggests that they may have a role in the natural history of these lesions.

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