

The Density of Mast Cells in Vascular Proliferations

VASKÜLER PROLİFERASYONLARDA MAST HÜCRESİ YOĞUNLUĞU

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Summary

Background: The etiology of acquired vascular proliferations remains obscure. In recent years, mast cells have been implicated to have causal role in the angiogenesis of vascular tumors.

Objective: The aim of the present study was to investigate the density of mast cells in common vascular lesions.

Patients and Methods: Formalin-fixed, paraffin-embedded lesional skin biopsies from 48 patients were stained with Giemsa and histopathologically studied for mast cell count. The study group consisted of 25 cherry angiomas, 8 capillary hemangiomas and 15 pyogenic granulomas. Two different control groups were utilized: the perilesional skin (intracontrol) and normal skin (intercontrol) from 12 healthy individuals.

Results: The mean number of mast cells was found as 12.96 ± 5.27 in cherry angiomas, 10.42 ± 9.87 in pyogenic granulomas, $10,31 \pm 8.24$ in capillary hemangiomas, and 9.93 ± 4.60 in normal skin. The mean lesional mast cell count was increased in pyogenic granuloma, cherry angioma and capillary hemangioma as compared with the perilesional and normal skin. The difference was statistically significant solely for cherry angiomas. ($p=0.001$, $p=0.049$).

Conclusion: Our results implicate a positive correlation between the mast cell density and vascular proliferations, although the exact role of mast cells in vascular lesions remains to be determined.

Key Words: Mastcells, Angiogenesis, Neovascularization

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Özet

Giriş: Vasküler proliferasyon ile seyreden akkiz lezyonların etyolojileri henüz tam olarak bilinmemektedir. Son yıllarda mast hücrelerinin vasküler tümörlerde anjiogenezden sorumlu olduklarına dair veriler elde edilmiştir.

Amaç: Bu çalışmada sık görülen vasküler lezyonlarda mast hücre yoğunluğunun belirlenmesi amaçlanmıştır.

Hastalar ve Yöntem: Toplam 48 hastaya ait 25 cherry anjiyom, 15 pyojenik granülom ve 8 kapiller hemanjiyom lezyon örneği Giemsa ile boyanarak mast hücre sayısı değerlendirilmiştir. Kontrol grubu olarak perilezyonel deri ve 12 sağlıklı kişiden elde edilen normal deri örnekleri kullanılmıştır.

Bulgular: Lezyonel deride ortalama mast hücre sayısı cherry anjiyomda 12.96 ± 5.27 , pyojenik granülomda 10.42 ± 9.87 , kapiller hemanjiyomda $10,31 \pm 8.24$, normal deride ise 9.93 ± 4.60 olarak tespit edilmiştir. Her üç tip vasküler lezyonda da lezyonel ortalama mast hücre sayısı perilezyonel ve normal deriden fazla bulunmuş, ancak istatistiksel anlamlılık yalnızca cherry anjiyomda saptanmıştır ($p=0.001$, $p=0.049$).

Sonuç: Bulgularımız vasküler lezyonlarda mast hücre yoğunluğunun arttığı hipotezini desteklemektedir. Ancak bu hücrelerin vasküler lezyonlardaki gerçek rollerinin araştırılması gereklidir.

Anahtar Kelimeler: Masthüresi, Anjiyogenezis, Neovaskularizasyon

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Mast cells (MC) play an important role in diseases such as hypersensitivity reactions, atopic dermatitis and contact dermatitis (1). An increase in the density of MC has also been demonstrated in bullous pemphigoid, psoriasis and cutaneous carcinomas (2). MC are found particularly along the arteries and capillaries in the dermis and

subcutaneous tissue (1,3,4). The tendency for accumulation around arteries has been observed by many authors and several studies have been performed to enlighten the role of MC in angiogenesis (1, 5, 6). It has been postulated that MC and their products contribute to the growth of vascular endothelium.

The aim of the present study was to investigate the MC densities in benign vascular proliferations frequently encountered in clinical settings, namely pyogenic granuloma, capillary hemangioma and cherry angioma.

Patients and Methods

Patients and Control Group

This study was designed as a prospective study including 48 consecutive patients with vascular lesions diagnosed and totally excised at the Dermatology Department of Kırıkkale University Faculty of Medicine between September 1998 and December 2001. Briefly, the diagnosis of vascular proliferations was based on typical clinical, dermatoscopic and histopathological features. According to the clinicopathological diagnosis, 25 biopsy samples were cherry angiomas, 8 were capillary hemangiomas and 15 were pyogenic granulomas. Control skin samples were obtained from 12 healthy subjects who provided informed consent for biopsy of non-lesional skin.

Methods

Biopsy samples were fixed in 10 % formalin and embedded in paraffin. Six micron-thick sections were obtained by microtome and stained with hematoxylin-eosin and Giemsa. The slides were histopathologically reviewed by one of the authors (PA) and analyzed quantitatively for the mean number of mast cells. MC were readily identified by the presence of intracytoplasmic metachromatic granules. The number of MC have been determined a) within the lesion b) within perilesional area of the lesional biopsy samples c) within normal skin biopsy samples. In each slide, the number of MC per high power field (X 400) in the center of the main lesion have been counted by light microscope (Leica) in ten areas. The quantitative determination of MC in the perilesional skin and in normal skin biopsy samples have been performed similarly. For normal skin, the average MC density was determined throughout the dermis. Mean MC count for each slide was obtained by dividing the total number of MC by the total number of areas examined.

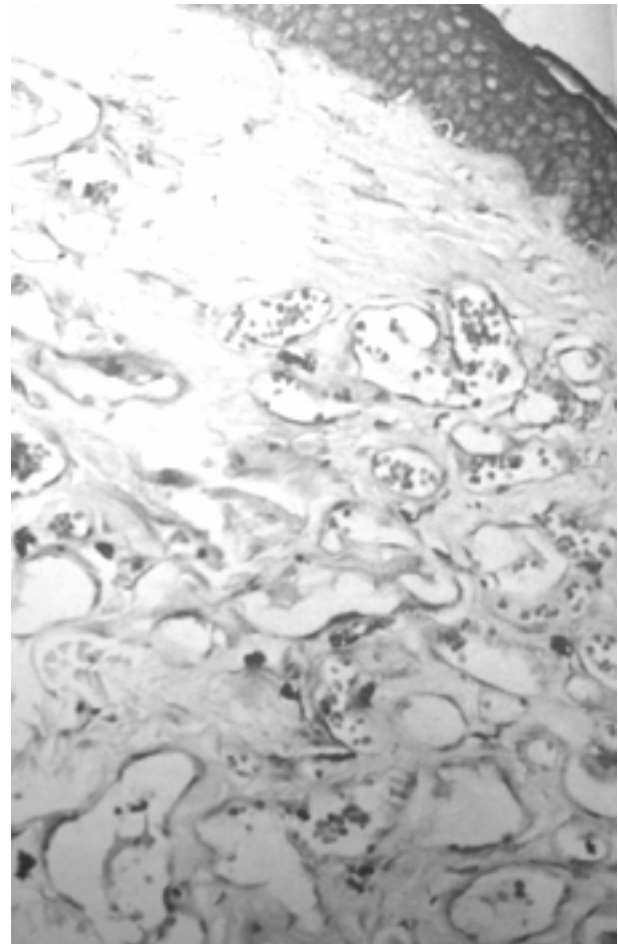


Figure 1. Giemsa staining of mast cells in cherry angioma (X 100).

Statistical Analysis

The results of the study were statistically analyzed using SPSS 10.0 program (Windows, Microsoft, USA). Wilcoxon matched pairs test has been utilized for comparison of the mean MC count in lesional, perilesional and normal skin. A p value of ≤ 0.05 was considered significant.

Results

For all 3 types of vascular proliferations, MC density was pronounced in the center of the lesions, with a tendency for a reduction in MC count towards the periphery of the lesions.

The mean lesional and perilesional MC count in cherry angioma (n=25) were 12.96 ± 5.27 (min: 2.1; max: 25) and 5.4 ± 2.12 (min:1; max: 10) respectively. The mean number of mast cells in nor-

mal skin was 9.93 ± 4.60 (min:4.70; max: 20.5). Statistical analysis showed that MC count was significantly increased in cherry angioma as compared with the perilesional ($z = -4.775$; $p = 0.001$) and normal skin ($z = -1.964$; $p = 0.049$).

The mean lesional and perilesional MC count in pyogenic granuloma ($n = 15$) were 10.42 ± 9.87 (min: 0.8; max: 30.5) and 6 ± 3.13 (min: 0.5; max: 11) respectively. The mean MC count of pyogenic granuloma did not reveal a significant difference when statistically compared with the perilesional ($z = -0.182$; $p = 0.878$) and normal skin ($z = -1.440$; $p = 0.152$).

The average lesional and perilesional MC count in capillary hemangioma ($n = 8$) were $10,31 \pm 8.24$ (min: 2.8; max: 24) and 7.1 ± 5.2 (min: 1.8 max: 15.2) respectively. Statistically, the mean MC number in hemangioma did not significantly deviate from that in perilesional ($z = -0.113$; $p = 0.856$) and normal skin ($z = -1.602$; $p = 0.145$).

Discussion

Mast cells are located mainly in connective tissue and have been shown to accumulate near sites of new capillaries (1,7). Because of their recruitment to sites of neovascularization, a potential role in angiogenesis was proposed. The process of angiogenesis is regulated by numerous factors including growth factors and integrins (7). Although the exact mechanism of MC-associated angiogenesis is not completely known, MC have been shown to secrete several mediators that might contribute to vascularization, including heparin, histamine, $TNF-\alpha$, $TGF-\beta$, basic fibroblast growth factor and tryptase (1,8). It has been observed that these MC-derived products stimulate proliferation of microvascular endothelial cells and promote endothelial cell tube formation (8). The study of Blair et al (7) confirmed the role of mast cells in capillary growth and specifically identified tryptase, a MC-specific secreting granule, as an important factor in regulating angiogenesis. In addition, the authors detected diminution of capillary growth with specific tryptase inhibitors.

Looking specifically at the studies investigating the role of MC in vascular lesions, Lascano et

al could not find any difference between the number of MC in capillary hemangiomas and normal skin (9). In contrast to this observation, many studies suggest an increased mast cell density in benign cutaneous vascular proliferations. Baroni et al (10) have demonstrated a significant increase in the number of MC in hemangiomas and Belcher et al (11) have found increased number of MC in angiolipomas. Glowacki and Mulliken (4) found increased number of MC in capillary hemangiomas. Hagiwara et al (1) have shown a significant increase in the average density of MC in pyogenic granulomas as compared with the normal skin. These findings suggested a role for MC in the angiogenesis of vascular tumors (1,4,12). Our findings are in accordance with the previous data, implying that the average MC count is increased in benign vascular proliferations of the skin.

Capillary angiomas have been classified into 7 groups according to the dynamic developmental stages as origin, initial growth, intermediate growth, completed growth, initial involution, intermediate involution and completed involution stages respectively (4,13). Glowacki and Mulliken (4) found abundant MC in the proliferating phase of hemangiomas, but very few MC in the involuting stage. The authors speculated that the formation and maintenance of hemangiomas mainly depend on a large concentration of MC, whereas reduction of the stimuli from MC results in involution of the lesions. Pasyk et al (13) reported that MC count was greater particularly in completed growth and initial involution phases of capillary angiomas. They stated that the increase in the number of MC was associated with the gradual formation of fibrous tissue within the lesion. Contrary to Glowacki and Mulliken (4), Pasyk et al (12) believe that MC are not responsible for the proliferation of the vascular endothelium, but rather for the gradual growth of fibrous connective tissue inside the tumor, reflecting the tissue repair and subsequent regression. These authors proposed that MC accumulation precedes the involution stage of hemangiomas and the number of MC considerably decrease as the hemangioma is replaced by fibrous connective tissue.

In the present study, the MC densities in benign vascular proliferations were determined on slides stained with Giemsa, which reveals higher mast cell profiles than does the toluidine blue stain (14). We found that the mean MC count in cherry angioma, pyogenic granuloma and capillary hemangioma were increased, compared to the perilesional and normal skin. However, the increase in MC count was statistically significant only for cherry angioma. The basis of insignificant results for pyogenic granuloma and capillary hemangioma may potentially be attributed to the statistical bias caused by the low number of specimens available for analysis. Nevertheless, our study suggests that MCs may act as potential factors/ cofactors in the development of cherry angiomas. As far as we know, there has been no previous study demonstrating a significant increase in MC density in cherry angiomas. A few available studies (1) were limited by a small number of samples inappropriate for statistical analysis. Whether the expansion of mast cell count is an inherent feature of vascular proliferations during the initial growth phase or represents a secondary phenomenon occurring during the regression stage remains to be determined. Nevertheless, the relative persistence of cherry angiomas without a tendency for involution might suggest that MC may have a potential role by promoting angiogenesis in these common lesions. Further studies on a large number of biopsy specimens will clarify the exact role of MC in benign cutaneous vascular lesions.

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