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Research Article

The Nature Of The Cavernous Hemangioma and Comparison Mr Image and Ki–67 Proliferating Index

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Abstract

The pathogenesis of cerebrovascular malformations is currently unknown. Lately recent researchs suggest that their pathogenesis and development might be due to various factors taking part in the angiogenesis. Cavernous hemangiomas (CHs) are considered as dynamic lesions. Until now, in the relevant literature only four studies about anti-Ki–67 proliferating index (MIB–1) of CHs have been cited. The mainstay of this study is definition of Ki–67 reactivity in CHs.Ten paraffin embedded sections stained immunohistochemically with antibodies to Ki–67 were analyzed. In this study MRI of the 10 CH's were grouped according to the Zabramski's classifications. According to Zabramski's classification distribution of our cases were type I 4 cases, type II 3 cases and type III 3 cases. Labeling index for Ki–67 were found to be immunopositively reacting in endothelial cells of 4 cases of CHs (40%) (2 type I; 1 type II, 1 type III). The relation between MRI and Ki–67 proliferative index were similar and there was no relation between the types of CHs regarding with MRI classification of Zabramski.

Keywords: Cerebrovascular malformations, cavernous hemangioma, Ki–67, immunohistochemistry

Kavernöz Hemangiomaların Doğası ve Mr Görüntüleri İle Kı-67 Proliferatif İndeksinin Karşılaştırılması

Özet

Kavernöz hemangiom (KH)'ların gelişimsel ve patolojik mekanizma(lar)sı birçok araştırmacı tarafından belirlenmeye çalışılmış olsa da halen kesinlik kazanmış değildir. KH endotelinin anjiogenetik ve proliferatif kapasitesi son zamanlarda "proliferating nuclear cell antigen" (PCNA), MIB–1, "vascular endothelial growth factor" (VEGF) ve VEGF reseptörü (VEGF-R) Flk-1 immünohistokimyasal çalışmaları ile ortaya konmuştur. Literatürde KH'lerde anti-Ki–67 proliferatif indeksi (MIB-1) iki çalışmada sorgulanmış olup bunların hiçbirinde KH endotelinde reaktivite izlenmemiştir. Bu çalışmada Marmara Üniversitesi Nörolojik Bilimler Enstitüsü'nde (M.Ü.N.B.E) 1998-2002 yılları arasında tanı almış 13 KH olgusuna Ki-67 uygulanmıştır. Olgular MR görüntüleri bakımından Zabramski sınıflamasına göre gruplandırılarak Ki-67 sonuçları bakımından karşılaştırılmıştır. Olgulardan 10'unun MRG filmlerine ulaşılabilmiştir. Buna göre TIP-I (4 olgu), TIP-II (3 olgu), TIP-III (3 olgu) olarak belirlenmiştir. Anti Ki–67 işaretleyicisi olan MIB-1 ile 5 (%38) (2 TIP-I; 2 TIP-II, 1 TIP-III) KH olgusunda endotel hücrelerinde immünreaktivite izlenmiştir. Pozitif olguların gruplara göre dağılımında ise özellik izlenmemiştir.

Anahtar Kelimeler: Serebrovasküler malformasyon, kavernöz hemangiom, Ki-67, immünhistokimya

INTRODUCTION

Cavernous hemangiomas (CHs) are the lesions that occurred due to embryonic maldevelopment of the brain or the menings[7,9,14,20]. CHs have neither neural parenchyma nor large feeding and draining vessels. It contains thin layer capillary like irregular channels and also called hamartomas[9]. CHs are frequent lesions with 0,3–0,5 % prevalence. It's known that the CHs are the 10–20 % of all cerebral vascular malformation (8,13). The mean length is 34 mm, and means volume is 2779+- 560 mm3. The mean age is 34[2]. CHs are diagnosed supratentorial (80 %), infratentorial (15 %), spinal cord (5 %) and rarely at cranial nerves[3,8,13]. After the increase of the role of MRI, the prevalence of the CHs was published 0,5 % and 18,7 % of CHs were multiple. MRI (Magnetic Resonance Imaging) helps to diagnose the CHs. Zabramski classified CHs as four types[20]. In the literature, there is no trial about the comparing of MRI and Ki–67 proliferations or any other proliferative marker. In this trial, we compared the MRI findings with Zambraski classified types of CHs and Ki–67 staining of vascular endothelium.

METHODS

Ten CH cases diagnosed in Marmara University Institute for Neurological Sciences pathology laboratory in between 1995–2003 years were studied. Representative sections of the lesions were selected and cut to 2 μm, and stained with Ki–67. They were grouped according to Zabramski classification (Table 1) with the help of MRI findings (ref 20).

Immunohistochemistry

Immunohistochemical staining was performed on formalin-fixed, parafin-embedded tissue following heat-induced epitope retrieval. Sections prepared on 3 aminopropyltriethoxysilane-coated slides were deparaffinized at 60°C in microwaves at 1 hour, incubated in xylene and alcohol, washed. Immersen in 0.01-mol/L sodium citrate buffer, and exposed to microwave for 15 min at 100% maximum power. Then for 20 min. at %50 maximum powers in an 800-W microwave oven was used. Following incubation with primary antibody (monoclonal MB67, dilution 1/1000 Neomarkers, Fremont) and washing, detection was performed stretavidin-biotin technique. The sections were washed, counter stained with hematoxylin, dehydrated through graded alcohols, and then coverslipped with entallan™.

RESULTS

Our patients' age range was between the 21 and 53; six patients were male and four were female. The mean age was 34,6. According to Zabramski's classifications; type I, type II, type III are 4.3.3 case respectively (Figure 1 and 2).

Immunoreactivity with Ki–67 rates was 40 % (4 patients) (Figure 3). We had four patients in the first group with two positive staining of Ki–67, three patients in the second group with one positive staining of Ki–67, and three patients in the third group with one positive staining of Ki–67 (Table 2).

Table 1: Classification of CHs*

Type of CH	Appearance on MR Imaging
I	Hyperintense on T1, T2 weighted images
II	Reticulated core of mixed signal intensity with a surrounding hemosiderin ring on
	T1 and T2 weighted images
III	Iso-to hypointense on T1 and T2 weighted images
IV	Poorly visualized, except on gradient-echo images

*As described by Zabramski (ref 20)

Table 2: Clinical and Demographic Data of Patients and Ki–67 Index

No	Y/S	Location	MR Type	Ki–67
1	37/F	Temporal	II	Negative
2	30/F	Frontal	I	Sparse positive
3	49/M	Orbita	III	Pozitive
4	53/M	Precantral gyrus	I	Sparse positive
5	21/F	Frontal	I	Negative
6	26/M	Frontal	III	Negative
7	30/M	Temporal	III	Negative
8	21/F	Parieto-temporal	II	Negative
9	49/M	Occipital	I	Negative
10	30/M	Occipital	II	Sparse positive

DISCUSSION

The clinical features and de novo synthesis[2,8,9,13,20] of CHs are described in many trials. Notelet et al established after staining with PCNA that CHs are dynamic lesions[10]. De novo lesions cerebral vascular malformation may bleed due to undiagnosed lesions of brain. Genetically intense patients may show increased cell proliferation due to secondary mutation. This considers high inheritance rate of CHs and other genetically mutations may be with CHs[10].

There are some trials in the literature that support the de novo synthesis of CHs. First CHs may occur at the radiated areas of brain[2]. Second, endothelial cells of CHs are highly stained with Ki–67 and PCNA when it's compared with normal vascular endothelium[4,15]. Third, CHs may occur in the way of biopsy[2]. Last, CHs may enlarge or occur in different areas with the effect of hormones[12]. The increasing volume of CHs is much more frequent that the possible hemorrhage rate (3 % / year) [11]. There are same trials in the literature about CHs relation to integrins, structural proteins and angiogenic factors[1,5,16,18,19,21]. But there are not so many trials in the literature about CHs and Ki–67[6,15,17]. Sure U. et al published the MIB–1 immunoexpression of AVM with 12 %, but no staining for CHs[15]. There is some trial that reveals the Ki–67 staining of CHs. In other study of the Sure U. et al, positive immunostaining of endothelial cells occurred in 38% of the cases for Ki–67[17]. Maiuri F. et al published the expression of Ki–67 were always absent in stable lesions, and it was positive in eight (72,7%) of 11 aggressive lesions[6]. Zehao Y showed no Ki–67 immunoexpression in CHs in is trial[21]. In our trial we show Ki–67 positivity 40 % in patients with CH.

According to Zambramski classifications type IV lesions are similar to capillary telangiectasia[20]. It is difficult to determine the type IV CHs and capillary telangiectasia. Unlike the small CHs, the capillar telangiectasia is contrast enhancing with gadolinium. Also capillary telangiectasias are larger than type IV CHs[14]. In our trials, in all types of the CHs, Ki–67 proliferations was similar. It should support with large series. MRI and Ki–67 proliferate index relation were similar and there is no relation had seen between the types of CHs regarding to MRI classification of Zabramski.

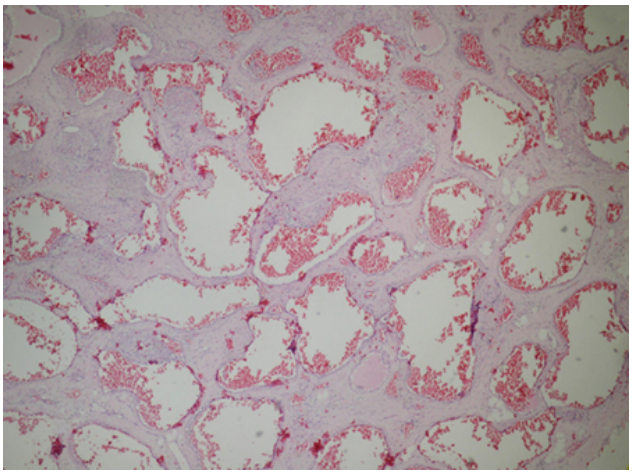

Figure 1: *Cavernous hemangioma, H&E X40*

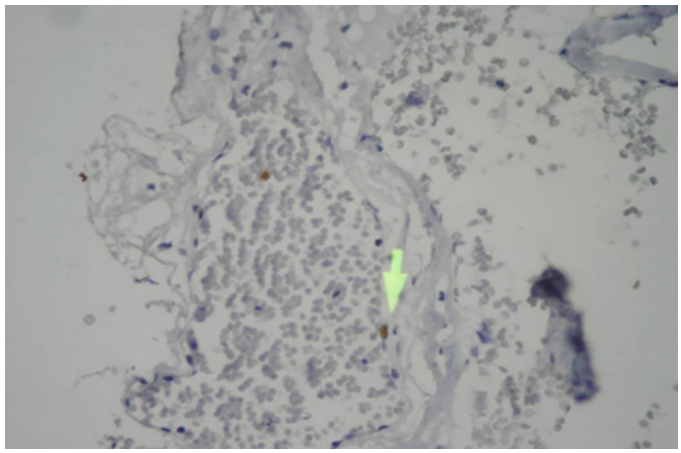

Figure 3: *Ki-67 staining of endothelial cells (X200 Original magnification, biotinylated streptavidin)*

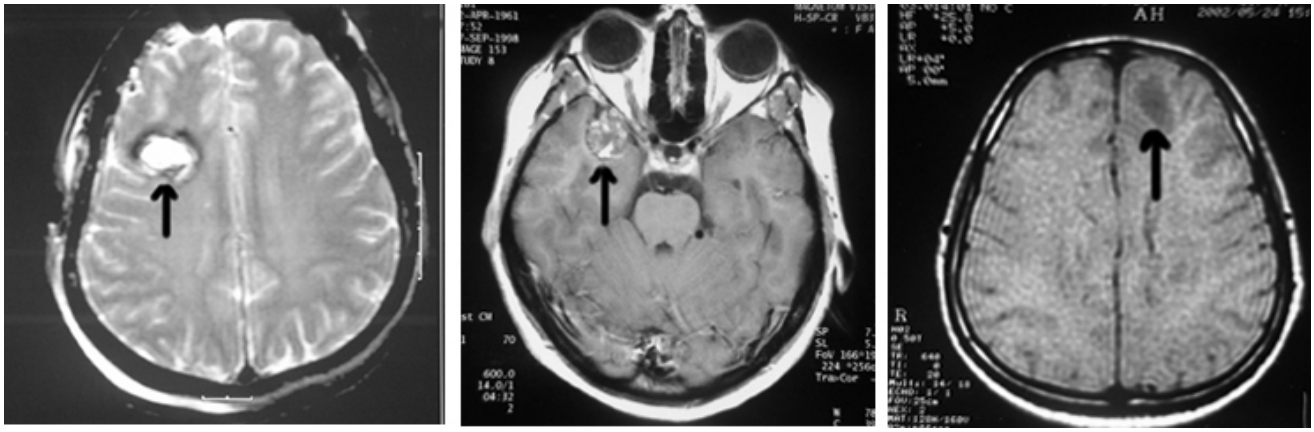

Figure 2: *Type I, II, III MR image*

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