Pathological Pattern of Atypical Meningioma: Diagnostic Criteria and Tumor Recurrence Predictors

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Abstract

Purpose

This study aimed to verify the pathological pattern of atypical meningioma according to the WHO 2007 grading criteria and to identify possible predictors of tumor recurrence.

Patients and methods

This is a hospital based study conducted at the National Center of Neurological Sciences- Khartoum during 2007-2012. All patients operated upon and verified histologically as cranial atypical meningioma were considered. Histologic diagnosis supplemented with immunohistochemistry using epithelial membrane and progesterone markers were used. Review of cellular changes according to WHO 2007 diagnostic criteria was adopted in all cases. Patients with recurrent atypical meningioma plus a control group of non-recurrent atypical meningioma were further processed to immunostaining for detection of Ki67 antigen.

Results

Forty four patients were diagnosed having atypical meningioma, of which twelve patients were recurrent cases. The histologic and immunohistochemical verification of the cells study showed increased mitosis, high small cell components with high nuclear cytoplasmic ratio and tumor necrosis as predominant histological features of atypical meningioma. Association of high nuclear cytoplasmic ratio, mitosis and hyper cellularity with increased Li Ki67 as strong predictors of tumor recurrence.

Conclusions

Small cell components with high nuclear cytoplasmic ratio, increased mitotic figure and areas of necrosis are strong histological criteria for diagnosis of atypical meningioma while coexistence of Li Ki 67 is a predictor for tumor recurrence

Key words:

Atypical meningioma, Li Ki67, WHO 2007 histological criteria, tumor recurrence.

PATHOLOGICAL PATTERN OF ATYPICAL MENINGIOMA: DIAGNOSTIC CRITERIA AND TUMOR RECURRENCE PREDICTORS **Mohamed A.R Arbab , Sawsan A Aldeaf, Lamyaa A M El Hassan, Beshir M Beshir , Alsadeg F.B. Gassoum & Ahmed M El Hassan**

P a g e | **843**

Introduction

Meningiomas are common tumors of the CNS that originate from the meningeal coverings of the brain and spinal cord; it derives from the arachnoid cap cells. It accounts for about 30% of all primary brain tumors. The annual incidence of meningioma is estimated at 5 per 100 000 individuals. There is distinct gender preponderance towards women with a female to male ratio of about 2:1.Although most meningioma are benign, however, they have a broad spectrum of clinical characteristics and histologically distinct subtypes that are associated with high risk of recurrence, even after microscopic complete resection [1,2].In rare instances, meningioma are malignant. The WHO classification aims to better predict the divergent clinical characteristics of meningioma with a histological grading system based on statistically significant clinicopathological correlations.

There are three types of meningioma according to WHO 2000 grading classification grade1 which is considered benign, grade 11 that are intermediate and grade 111 which is malignant. This classification has set certain morphological criteria to classify the pathological characteristics of meningioma [3]. The current version of WHO classification was updated in 2007; it divided meningioma into three groups based on morphological criteria which have important implications on patient's management [4].

 In spite of the adopted WHO 2007 scale, still prediction of the biological behavior of meningioma remains a challenge.

Immunohistochemical studies using Ki 67 have been done to outline the predictive correlation of Ki 67 with histological grading and tumor recurrence [5, 6]. In Sudan cranial meningioma is the most encountered cerebral neoplasm. The atypical variant amounts to 30% of all meningioma and poses a clinical challenge since it is associated with relatively high risk of tumor recurrence.

General objective:

To identify the immunostaining reactivity of ki67 antigen in atypical (grade 11) meningioma among Sudanese patients.

Specific objectives:

1/ to identify the atypical histological criteria of meningioma among Sudanese patients according to WHO criteria 2007.

2/ to verify ki67 antigen labeling index, in atypical meningioma among Sudanese patients.

3/ to correlate the atypical features according to WHO criteria 2007 and ki67 antigen labeling index.

Clinical Material and methods

This is a prospective study done at the National Center of Neurological Sciences (NCNS) - Khartoum during the period 2007-2012. All patients operated upon for cranial tumors and the histopathology confirmed the diagnoses of atypical meningioma were considered in the study. Tumor specimens were processed for histologic diagnosis of meningioma. Immunohistochemistry using epithelial membrane antigen (EMA) and progesterone markers were used to confirm diagnosis of atypical meningioma.

PATHOLOGICAL PATTERN OF ATYPICAL MENINGIOMA: DIAGNOSTIC CRITERIA AND TUMOR RECURRENCE PREDICTORS **Mohamed A.R Arbab , Sawsan A Aldeaf, Lamyaa A M El Hassan, Beshir M Beshir , Alsadeg F.B. Gassoum & Ahmed M El Hassan**

P a g e | **844**

The diagnosis of atypical meningioma was made according to 2007 WHO criteria, which are defined as:

❖ The tumor contains 4 or more mitotic figures per 10 high power fields (0.16 mm).

❖ The tumor exhibiting at least three of the following features:

A/ Hyper- cellularity.

B/ Pattern less sheet- like growth.

C/ Macronuclei.

D/ Small cell components with high nuclear cytoplasmic/ratio.

E/ Zones of necrosis.

In another setting all recurrent atypical tumors (12 cases) plus 16 random non recurrent atypical cases were selected. The atypical features for each case were studied using immunostaining for ki67 antigen according to Dako standard protocol. Paraffin embedded blocks were sectioned 4 µm thick. These were then mounted onto special immunostaining slides and then incubated in the oven at 65° C for overnight. The slices were then treated with xylene, absolute ethanol, 90% ethanol, 70% ethanol respectively, and then washed in tap water. The sections were placed in target retrieval solution high pH (50 xs) at 95 ^{o}C in water path for 30 minutes (Dako Denmark A/S, productionsvej 42 DK-2600 Glostrup, Denmark)**.** Dako pen was used for drawing a circle around the reaction area on the slides. The slides were then placed in washing buffer for 10 minutes, followed by hydrogen peroxide for peroxidase blocking, and then washed in washing buffer for 15 minutes. , The primary antibody was added to all sections for 30 minutes, then washed in buffer for 15 minutes, followed by link solution (HRP) for 25 minutes, and washed in buffer for 15 minutes, and then diluted DAB solution was added for 10 minutes, and washed twice in water and washing buffer respectively. Mayer's heamatoxyline was used as a counter stain and the slides were cover slipped using DPX mounting medium. All sections were examined under the light microscope. The MIB-1 LI is calculated as the percentage of tumor cell nuclei that stain positive out of the total number of tumor cell nuclei counted, as (>5%, <5% and –ve).

Data processing and statistical analysis

Data were analyzed using SPSS 13 software with reference P.value of 0.05 was considered statistically significant.

Results

During the period from 2007 to 2012 a total of 44 cases were operated upon for cranial tumor and diagnosed as atypical meningioma according to WHO 2007 criteria, accounting to 12% of the total number of cranial meningioma operated upon during the same period. Males constituted 38.9% and females 61 %. Parietal and frontal falx locations were the most common anatomical locations constituting 30.6% and 25.0% respectively. According to the WHO 2007 criteria, high nucleus to cytoplasmic ratio and increase mitotic figures were seen in 29 patients each (65.9%), followed by necrosis in 54.5% of the patients. Brain invasion was identified in 3 patients and bone invasion in 6 other patients and in other two patients inflammatory cells with lymphocytes infiltrate were identified (Table 1).

In the recurrent group (12 cases) and the random non-recurrent (16 cases) which was

PATHOLOGICAL PATTERN OF ATYPICAL MENINGIOMA: DIAGNOSTIC CRITERIA AND TUMOR RECURRENCE PREDICTORS **Mohamed A.R Arbab , Sawsan A Aldeaf, Lamyaa A M El Hassan, Beshir M Beshir , Alsadeg F.B. Gassoum & Ahmed M El Hassan**

P a g e | **845**

processed for Ki 67 immunostaining, positive immunostaining for Ki 67 antigen was identified in 27 cases (96.4%), and only one case was negative. The Li of Ki 67 antigen was calculated as (>5% and <5%) of positive cells nuclei out of the total number of tumor cells. Seventeen of the cases showed Li Ki 67 of >5% constituting (62.9%). and 10 of the cases were <5% (Table 2).

Positive immunostaining for Ki 67 was identified in 14 cases (66.6%) with sections showing high nuclear cytoplasmic ratio, 13 patients (61.9%) with increased mitotic figure and in 11 patients (52.3%) with tumor necrosis (Fig. 1).

Within the twelve patients (42.8%) with tumor recurrence, the dominant WHO 2007 criteria, were high nuclear cytoplasmic ratio (75%), increased mitotic figures (66.7%) and hyper cellularity in (58.3%) (Table 2).

Discussion

Meningioma has been recognized as a tumor entity for nearly 200 years. It accounts for 24-30% of intracranial tumors and they are considered mostly as benign [3]. A significant minority are atypical (WHO Grade II). Whole older series put the proportion of atypical meningioma at 5-7%; the actual proportion using the current WHO definitions is probably 15-20%.

Before the 2000 WHO classification scheme, several subjective classification systems existed. The (2000 WHO) grading system reclassified meningioma, creating standard diagnostic criteria, including WHO Grade II (atypical) meningioma, that is composed of ; ≥4 mitotic cells per 10 hpf and/or 3 or more of the following: hyper cellularity, small cells, necrosis, prominent nucleoli, and sheeting.

Further revision of the WHO scheme in 2007 included brain invasion in an otherwise Grade I tumor as an additional criterion for a WHO Grade II lesion [4]. This recent WHO 2007 classification provides broad criteria for differentiating benign and atypical meningioma, with hyper cellularity and increased mitotic index as possible predictors for recurrence. Necrosis and focal necrosis have also been regarded as indicators of recurrence. Some studies has reported on the histological features of meningioma and the genetic predisposition to the disease [7,8,9]. Numbers of macrophages and T and CD8 lymphocytes in meningioma have been related to atypical histology [10].

In the present study, we adopted the above WHO 2007 grading criteria. The histopathological criteria for the accurate interpretation of atypical meningioma have been well adopted as defined in this study. This scoring system clearly distinguished benign and atypical variants of meningioma. It is being emphasized that neuro pathologists should be familiar with these criteria and the scoring system. In addition, an accurate interpretation of the atypical meningioma is essential since these tumors are likely to recur much earlier than benign and may necessitate adjuvant radiotherapy as treatment modality.

Results of this study have shown that the atypical meningioma (WHO Grade II) constituted 9.4% of all meningioma that were seen during a five year period 2007-2012 at the NCNS. They were diagnosed using the WHO 2007 morphological criteria. In the present series, small cell components with

PATHOLOGICAL PATTERN OF ATYPICAL MENINGIOMA: DIAGNOSTIC CRITERIA AND TUMOR RECURRENCE PREDICTORS **Mohamed A.R Arbab , Sawsan A Aldeaf, Lamyaa A M El Hassan, Beshir M Beshir , Alsadeg F.B. Gassoum & Ahmed M El Hassan**

P a g e | **846**

high nuclear to cytoplasmic ratio and increased mitotic figures were the most common features seen, followed by necrosis and to less extent the other remaining criteria. The histological criteria in the recurrent specimens are observed in order of frequency, high nuclear to cytoplasmic ratio in 75%, increased mitotic figures in 66.7% and hypercellurarity in 58%. The other criteria are less frequent. Furthermore the histological patterns of the recurrent tumors and the Ki67 Li have distinct association. While small cell components with high nuclear to cytoplasmic ratio, increased mitotic figures and tumor necrosis seem to be strong histological indicators of atypical meningioma, co-existence of Ki 67 Li and/or small cell components with high nuclear cytoplasmic ratio, increased mitosis and hyper cellularity are strong predictors of tumor recurrence. Accurate histopathological diagnosis of atypical meningioma is essential for predicting the recurrence and biological behavior as well as for planning post-operative treatment modalities. Large scale series is needed to consolidate the results of this study. The frontal and falx areas were the most common sites affected followed by the temporal area, CPA and sellar regions. The anatomic location does not seem to influence the biological behavior of the tumor.

Conclusion

In conclusion the present study suggests that small cell components with high nuclear cytoplasmic ratio, increased mitotic figure and areas of necrosis are strong histological criteria for diagnosis of atypical meningioma

while coexistence of Li Ki 67 is a predictor for tumor recurrence.

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PATHOLOGICAL PATTERN OF ATYPICAL MENINGIOMA: DIAGNOSTIC CRITERIA AND TUMOR RECURRENCE PREDICTORS **Mohamed A.R Arbab , Sawsan A Aldeaf, Lamyaa A M El Hassan, Beshir M Beshir , Alsadeg F.B. Gassoum & Ahmed M El Hassan**

P a g e | **847**

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PATHOLOGICAL PATTERN OF ATYPICAL MENINGIOMA: DIAGNOSTIC CRITERIA AND TUMOR RECURRENCE PREDICTORS **Mohamed A.R Arbab , Sawsan A Aldeaf, Lamyaa A M El Hassan, Beshir M Beshir , Alsadeg F.B. Gassoum & Ahmed M El Hassan**

P a g e | **848**

Figures and Tables

Fig. 1 Positive immune staining for Ki 67 showing Li Ki67 >5% (A) and <5% (B). (X40)).

A   B
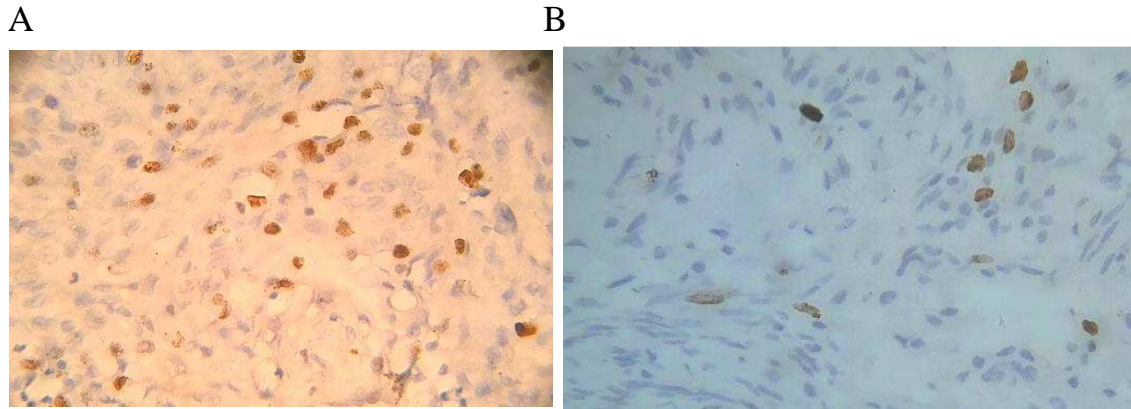
Table 1   WHO 2007 histological criteria of 44 patients with atypical meningioma

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Histologic criterion	Number of cases	%
Increased mitosis	29	65.9
Hyper cellularity	16	36.4
Macronuclei	21	47.7
High nuclear to cytoplasmic ratio	29	65.9
Necrosis	24	54.5
Hyperchromasia	13	29.5
Nucleoli	3	6.8
Brain invasion	3	6.8
Bone invasion	6	13.6
Inflammatory cells	2	4.5
Total	44	100

PATHOLOGICAL PATTERN OF ATYPICAL MENINGIOMA: DIAGNOSTIC CRITERIA AND TUMOR RECURRENCE PREDICTORS **Mohamed A.R Arbab , Sawsan A Aldeaf, Lamyaa A M El Hassan, Beshir M Beshir , Alsadeg F.B. Gassoum & Ahmed M El Hassan**

P a g e | **849**

Table 2. WHO 2007 histologic criteria and Li Ki67 of 12 patients with recurrent atypical meningioma.

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Histologic criterion	Number of cases with positive Li Ki67		Total	%
	>5%	<5%		
Increased mitosis	6	2	8	66.7
Hyper cellularity	4	3	7	58.3
Macronuclei	4	1	5	41.7
High nuclear cytoplasmic ratio	7	2	9	75.0
Necrosis	4	1	5	41.7
Hyperchromasia	1	0	1	8.3
Nucleoli	1	1	2	16.6
Brain invasion	0	0	0	0
Bone invasion	0	0	0	0
Inflammatory cells	0	0	0	9
Total	27	10		

PATHOLOGICAL PATTERN OF ATYPICAL MENINGIOMA: DIAGNOSTIC CRITERIA AND TUMOR RECURRENCE PREDICTORS **Mohamed A.R Arbab , Sawsan A Aldeaf, Lamyaa A M El Hassan, Beshir M Beshir , Alsadeg F.B. Gassoum & Ahmed M El Hassan**

P a g e | **850**