American Journal of Medical Case Reports, 2018, Vol. 6, No. 5, 89-91
Available online at http://pubs.sciepub.com/ajmcr/6/5/4

DOI:10.12691/ajmcr-6-5-4

Magnetic Resonance Imaging Survey of Peri-tumoral Edema of Meningioma and their Correlation with Progesterone Receptor Expression in Iranian Population

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Abstract **Introuction:** Meningiomas represent the most common primary brain tumor and comprise 3 World Health Organization (WHO) grades, the most frequent being WHO grade I (90%). In this study, we aim to investigate the prevalence and features of peri-tumoral edema of these lesions on Magnetic Resonance Imaging and their relationship with progesterone receptor (PR). **Methods:** From August 2011 to December 2017, we have enrolled 281 patients diagnosed with meningiomas of central nervous system, who underwent thorough imaging evaluation of diameter, size, volume and peri-tumoral edema on MRI. Of these patients, 187 patients were candidates of either surgical resection of biopsy, who were evaluated for PR by histopathological examination and immunohistochemistry (IHC) study after surgical removal. **Results:** Authors have found that meningiomas with higher PR positivity, represents lower volumes and also they appear as less aggressive lesions on neuroimaging. Also, we have found that meningiomas with higher PR positivity in IHC study, represents lower peri-tumoral edema on T1- and T2-weighted MRIs. On the other hand, our surgical experience showed that patients with more PR positive meningiomas, exhibit prolonged disease, with lower rate of hemorrhages. **Conclusion:** In this study, we have found that meningiomas with higher PR positivity, represents lower peri-tumoral edema and thus lower neurological complications; However, more advanced histopathological examination for other receptors may improve prognosis determination.

Keywords: *meningioma, progesterone receptor, magnetic resonance imaging, histopathological examination*

Cite This Article: Zahra Janamiri, Vahid Shahmaei, and Yousef Moghimi Boldaji, "Magnetic Resonance Imaging Survey of Peri-tumoral Edema of Meningioma and their Correlation with Progesterone Receptor Expression in Iranian Population." *American Journal of Medical Case Reports*, vol. 6, no. 5 (2018): 89-91. doi: 10.12691/ajmcr-6-5-4.

1. Introduction

Harvey Cushing has described the term "meningioma" as tumors that rise contiguous to the meninges. Most of them of benign and encapsulated tumors, while genetic mutations, intracranial and spinal anatomical location and their volume may change their benign course to unfavorable prognosis. [1] Meningiomas are the most frequently diagnosed primary tumors of brain, accounting for 33% of all primary brain neoplasms of central nervous system from 2003 to 2006 in Unite States. Genetic susceptibility for meningioma development is either familial or sporadic as DNA repair gene failure. Also, certain mutations in neurofibromatosis gene (NF2) have a very substantial risk for meningioma development. [2] High dose ionizing radiation exposure is another risk factor for development of meningiomas, which this phenomenon has been observed with even low radiation doses. Moreover, based on epidemiologic studies, meningiomas are observed in female population twice as men, since etiologic roles of hormonal factors such as decreased or lost estrogen receptor expression is highly correlated with growth of benign meningiomas, while loss of progesterone receptor expression is an indicator of early recurrence. [3,4] Meningiomas have variable signal intensity and radiological features on Magnetic Resonance Imaging (MRI). Thus authors plan to investigate the prevalence and features of peri-tumoral edema of these lesions on Magnetic Resonance Imaging and their relationship with progesterone receptor (PR).

2. Methods

Authors have enrolled 281 patients who referred to neurology and neurosurgery departments of one of private hospitals in Tehran, with confirmed diagnosis of meningioma by neuroimaging, composed of either Computed Tomography (CT) scan or MRI. Of these patients, 187 patients are nominated for either surgical resection or biopsy. Authors have excluded patients with active malignancies who are receiving chemotherapy

regiments, patients with previous history of radiation exposure, patients with previous history of cerebral surgical interventions, patients with intracranial malignancies and intracranial metastases, patients who their general health condition did not allow for safe surgical intervention, patients with confirmed diagnosis of specific syndromes with increased meningioma development chance (such as neurofibromatosis), patients with confirmed pregnancy and history of prolonged oral contraceptive pills receive and patients who failed to sign the written informed consent form. Written informed consent was prepared according to criteria of national Ethics Committee. Demographic data of patients were collected, and thorough evaluation of their MRI was performed by an expert neuroradioloist blinded to the study, for assessment of tumor size and volume, as well as their peri-tumoral edema on both T1 and T2-weighted sequences. Authors have performed targeted histopathological examination (including immunohistochemistry (IHC) study) of extracted tissues for PR expression.

3. Results

Of all 281 patients who were referred to neurology and neurosurgery departments, we have excluded 94 patients with confirmed diagnosis of meningioma, who were candidates of non-surgical treatments and follow-up. On the other hand, 187 patients with brain meningiomas have enrolled into the study, since they were suitable for further histopathological examinations. Surgical resection candidates were patients who accidentally found their tumor and were asymptomatic (54 patients) and patients who suffer from neurological deficits (112 patients). However, rest of the patients with their meningioma located near deep neurological structures and adjacent to brain stem, were nominated for biopsy for histopathological examination and staging for further treatment strategy (21 patients). Our patients were consisted of 121 females (64.7%) aged between 17.3 to 67.3 years (mean age 43.2 years) and 66 males (35.3%) aged between 23.2 to 63.2 years (mean age 38.7 years). MRI analysis revealed supratentorial location in 155 patients (83%), including parasagittal (88 patients), sphenoid ridge (32 patients), juxta sellar (20 patients) and olfactory groove (15 patients). Of the rest of the 32 patients, infratentorial and miscellaneous intradural meningiomas were observed in 24 (12.8%) and 8 (4.2%) patients, respectively. Intra-ventricular meningioma and optic nerve meningioma, as well as pineal gland meningiomas are accounted for miscellaneous groups. MRI investigation revealed T1-weighted iso-intensity in 134 patients (71.6%), followed by hypo-intense signals in 53 patients (28.4%). Also, T2-weighted imaging showed iso-intensity in 102 patients (54.5%), while hyper-intensity was observed in 87 patients (45.4%). Excised tissues from either surgical resection or biopsy underwent thorough histopathological and IHC examination for PR. Authors have found that meningiomas with higher PR positivity, represents lower volumes and also they appear as less aggressive lesions on neuroimaging. Also, we have found that meningiomas with higher PR positivity in IHC study, represents lower peri-tumoral edema on T1- and T2-weighted MRIs. On the other hand, our surgical experience showed that patients with more PR positive meningiomas, exhibit prolonged disease, with lower rate of hemorrhages.

4. Discussion

Meningiomas are non-glial neoplasms and are categorized as extra-axial tumors. They rise from meningocytes and arachnoid cap cells of the meninges. These lesions are usually benign with low recurrence and aggression rate, while histological variants of these lesions may exhibit favorable prognosis, to unpredictable and devastating outcomes due to their anatomical location and enhanced growth rate. [5] Although female to male predominance is reported in many studies, as we did, atypical meningiomas are more common in men population. Most of them are asymptomatic and may be discovered incidentally in a healthy individual, while larger tumors with their anatomical derangement or by peri-tumoral edema, may cause a wide range of neurological symptoms, such as headache which is the most common encountered symptom in these patients, followed by neurological deficits and altered mental status secondary to herniation, brainstem compression or hydrocephalus. [6] Since meningocytes and arachnoid cap cells of the meninges are originated from pluripotent mesenchymal progenitor cells, these precursor cells explain the common extra-dural anatomical location of these lesions. As noted before, menigiomas may be inherited through specific syndrome such as neurofibromatosis type 2, secondary to Merlin gene on chromosome 22, which is more common in young men. [7] These lesions are mostly globular with wide dural attachment on macroscopic examination. Microscopically, meningothelial (syncytial), transitional and fibroblastic represent the most common subtypes on histopathological examination. Mentioned common types of histological appearance of meningiomas, fell under World Health Organization (WHO) grade I. WHO grade II (atypical) meningiomas, represent as chordoid and clear cells on histopathological examination. Also, papillary and rhabdoid subtypes are frequent in WHO grade III (anaplastic) histopathological examinations. [8] Also, IHC study is helpful in diagnosis of these neoplasms, by detection of epithelial membrane antigen which is positive in 75 to 80% of patients. Also, IHC study of meningiomas is negative for Leu 7 antibodies, which is a frequent positive marker in schwannomas, and also for glial fibrillary acidic protein (GFAP). [9] Also, PR and somatostatin receptors are variably encountered in meningiomas, in which PR can be demonstrated in the cytosol of meningioma cells. Peri-tumoral edema is a frequent finding in neuroimaging in half of the patients diagnosed with meningioma. [10] Multiple factors have been described as an underlying mechanism, while many authors believe that multi-factorial etiology is the most likely cause, but it has not been confirmed yet. These factors include age, sex, size and volume, rate of growth, location and histological type. In this study, authors have evaluated the correlation between peri-tumoral edema and PR by neuroimaging and IHC study. [11] Proposed mechanisms for peri-tumoral edema of meningiomas are described as venous stasis, compressive ischemia, aggressive growth, secretory

histological subtype of meningioma and vascular epithelial growth factor. [12] In this study, we have performed thorough neuroimaging evaluation for extent of peri-tumoral edema and mass colume of the tumor, as well as IHC study for PR for description of underlying mechanism of this phenomenon, which has not yet been investigated before.

5. Conclusion

In this study, we have found that meningiomas with higher PR positivity, represents lower peri-tumoral edema and thus lower neurological complications; However, more advanced histopathological examination and IHC study for other receptors may improve prognosis determination.

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