Expression of progesterone receptors in meningioma patients: serial case

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Abstract

Meningioma is a tumor that arises from the meningotheial cells of the arachnoid membranes which are attached to the dura mater. Meningioma is one of the most common tumors found in people and occurs more commonly in women due to the link with the progesterone hormones. The risk of developing meningiomas is increased in patients who are exposed to exogenous progesterone such as hormonal contraceptives. This case report must be reported because the hormonal contraceptives are largely used in Indonesia and it is important to report this case. It is reported in three cases of female patients aged 58 years, 46 years, and 38 years with the main complaint of chronic progressive headache and decreased consciousness with left hemiparesis. All patients had a history of using hormonal contraceptives for more than four years. Head CT scans were carried out and obtained the results of extra-axial masses in the supratentorial region of all three patients. Therapeutic management was performed by resection with the result of immunohistochemistry of the three patients showing an expression of progesterone receptor > 90% in the tumor cell nucleus. Progesterone receptors were found in patients with meningioma. The expression of progesterone receptors on tumor cell nuclei is related to prognosis. A positive progesterone receptor will be adopted with a better prognosis. Hormonal therapy such as antiprogesterone can inhibit the genetic mutation of meningioma. Yet, it is not recommended because there is no significant clinical evidence.

Keywords: Meningioma; Resection; Progesterone Receptor.

1. Introduction

A brain tumor is a tumor that occurs due to the growth of abnormal cells in or around the brain organs. Brain tumors are the second leading cause of death in cancer cases that occur in children under 20 years of age. Brain tumors also cause the second death of all cancers in men aged 20-39 years, and brain tumors are the fifth leading cause of death of all cancer patients in women aged 20-39 years [1]. Of all types of cancers of the central nervous system, the prevalence of brain tumors covers about 85-90%. There is no epidemiological data for brain tumors in Indonesia. A study in Bandar Lampung reported that during the period 2009-2013 there were 173 patients with a diagnosis of brain tumor based on histopathological results. In that study, there were more female patients than men (1, 8, 1). The most common tumor types were meningioma (57.8%) and astrocytoma (28.9%) with the most tumor locations in the frontal region (30.1%) [1].

World Health Organization (WHO) defines a meningioma is a tumor originating from the Leptomeninges meningotheial (arachnoid) cells. These tumors can occur anywhere along with the location of the arachnoid cells, usually adhering to the inner surface of the dura mater. Meningiomas are the second most common tumor in brain tumors, >90% are benign,
slow growth, but meningiomas can also be aggressive, such as an invasion of the brain, grow close to the bone, and are at risk of recurrence [2]. The incidence of meningiomas in the world is about 24-30% of primary intracranial tumors. In the United States, the incidence of meningioma is confirmed by examination pathology is estimated at 97.5 per 100,000 population. In Indonesia, data on the incidence of central nervous system tumors, especially meningiomas, have not been reported every year [3].

2. Material and methods

Data at Saiful Anwar Hospital (RSSA) shows that meningioma is the highest intracranial tumor (42%) followed by glioma (40%). Data in the Department of Anatomical Pathology, FKUI / RSUPN Dr. Cipto Mangunkusumo (RSCM) showed that meningioma was the highest intracranial tumor (58.5%) followed by glioma (23.7%). The Dharmais National Cancer Hospital also provided data on the types of primary brain tumors that most were meningiomas at 37.2% followed by gliomas [3,4].

Meningiomas are more common in women, this is thought to be due to the role of female sex hormones, with the reported prevalence of estrogen (0-94%) and progesterone (40-100%) in the meningioma tissue [4]. In the year of 2016 WHO makes the classification of meningiomas into 3 classifications, namely grade I (Meningothelial, Fibrosis, Transitional, Psammatous, Angiomatous, Microcytic, Secretory, Limphoplasmocyte-rich, Metaplastic), grade II (Clear cell, cardioid, atypical), grade III (Rhabdoid, Papillary, Anaplastic).

In grade I meningioma the expression of progesterone receptors is stronger than in grades II and III. In grade, I meningioma, the expression of progesterone receptors ranges from 55% -80% and is significantly more in women than in men[3]. Meningioma location is often intracranial, namely 85-90% of the supratentorial area along the dural venous sinus, including areas of convexity (34.7%), parasagittal (22.3%), sphenoid (17.1%). The location of the meningioma can cause varied clinical symptoms and will determine the prognosis and choice of therapy, especially surgery [4].

Clinical symptoms that are often complained of in meningiomas, such as headache (36%), changes in mental status (21%), paresis (22%), and memory weakness (16%) [2, 4]. Meningioma tumorigenesis is associated with mutations in the neurofibromatosis 2 (NF2) gene located on chromosome 22 in nearly 66% meningioma. NF 2 is a tumor suppressor gene that is mainly expressed by the nervous system, including Schwan cells, neurons, astrocytes, and cells in the lens of the eye.

The mutation of the NF2 gene causes inactivation of MERLIN resulting in cytoskeletal reorganization and triggers the development of meningiomas. This analysis of the NF2 gene differs in different types of histology. There was a loss of heterozygosity (LOH) of the NF2 gene on chromosome 22 in 95% of fibroblastic meningiomas and only 33% in meningothelial meningiomas. The most common chromosomal abnormality in meningioma is monosomy chromosome 22. This disorder is found in almost all types of meningioma [4].

The diagnosis of meningioma is based on clinical symptoms, radiological examination of the head with contrast agents, and histopathology. The clinical symptoms vary depending on the location of the tumor, such as chronic progressive headaches and focal neurological deficits such as visual disturbances, diplopia, hemiparesis, seizures, and so on [2, 3, 4]. Radiological examination of the head in meningioma can also help make the diagnosis. On Computed Tomography (CT) scan of the head, the meningioma will appear as a homogeneous mass, gives an iso or hypodense image compared to the surrounding parenchyma, stings strong and dense contrast, and has a wide attachment to the dura border.
On magnetic resonance imaging (MRI) the head of the meningioma appears to show isointense in the T1 sequence, which stings strongly and is homogeneous after contrast administration. There is a characteristic appearance of the dura around the lesion which is called the “dura tail” [4]. A resection is a therapeutic option in meningiomas. Resection is performed to remove as much tumor tissue as possible along with any bone and dura mater that may be involved. Meningioma grade I is managed with total therapy. Atypical, malignant meningiomas, WHO grade III, malignant subtypes are recommended for adjuvant radiotherapy after surgery [4]. The assessment of the extent of the operation was based on the Simpson classification. This classification can determine the likelihood of recurrence. The following is Simpson’s classification with its sequence levels [4].

**Table 1** Rates of recurrence after resection based on Simpson’s criteria.

<table>
<thead>
<tr>
<th>Simpson Grade</th>
<th>Completeness of Reaction</th>
<th>10-year Recurrence</th>
</tr>
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<tbody>
<tr>
<td>Grade I</td>
<td>Complete removal including resection of the underlying bone and associated dura</td>
<td>9%</td>
</tr>
<tr>
<td>Grade II</td>
<td>Complete removal + coagulation of dural attachment</td>
<td>19%</td>
</tr>
<tr>
<td>Grade III</td>
<td>Complete removal w/o resection of dura or coagulation</td>
<td>29%</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Subtotal resection</td>
<td>40%</td>
</tr>
</tbody>
</table>

*Progesterone receptors* interact with specific short DNA sequences known as hormone-responsive elements (HRE). This interaction will also induce phosphorylation of *progesterone receptors* and *progesterone receptors* interact with the basal machinery of transcription involved in gene expression. After phosphorylation of the *progesterone receptor* from the transcription complex, the *progesterone receptor* will be relegated through the ubiquitin-proteasome path [7, 8, 9]. Meninges of normal adults express low levels of *progesterone receptors*, the majority of meningiomas express *progesterone receptors*. A decrease in the expression of *progesterone receptors* from low grade to high grade has been reported and meningiomas with negative *progesterone receptor* expression are more aggressive than positive ones [7].

3. **Case report**

The three cases were female patients aged 58 years, 46 years, and 38 years. The three patients came to the emergency room with complaints of the gradual loss of consciousness, progressive chronic headaches, projectile vomiting, and accompanied by hemiparesis in all three. All three patients had a history of using hormonal contraception > 10 years. From the examination of blood estrogen-progesterone levels, the normal results were obtained in all three. Radiological examination with CT scan of the head with contrast in these three patients showed that there was a supratentorial extra-axial solid mass accompanied by cerebral edema. In the first patient, the extra-axial period was multiple [figure 1]8, 9].

![Figure 2](image.png)

**Figure 2** Contrast CT scan of the head.

(a). CT scan of the first patient with multiple extra-axial solid masses in the right frontal, right temporal, right occipital, and left temporo-basal regions (b). CT scan of the second patient with an extra-axial mass in the right frontal lobe (c). CT scan of a third patient with a solid extra-axial broad base sphenoid. Tumor resection was performed in these three
patients with Simpson grade IV classification in the first patient and Simpson grade II in the second and third patients and histopathological examination was carried out in all three patients with the following results [figure 2].

Figure 3 Histopathological picture of meningioma.

(a) Histopathology of the first patient with Chordoid Meningioma results (WHO Grade 2). (b) Histopathology of the second patient with Transitional Meningioma (WHO Grade 1) results. (c) Histopathology of the third patient with Meningothelial Meningioma results (WHO Grade 1). In these three patients, it was followed by an immunohistochemical examination of Progesterone Estrogen Antibodies with the result that all three had receptors. Strong positive progesterone > 90% in tumor cell nuclei [figure 3].

Figure 4 Immunohistochemistry of progesterone receptors on (a) Chordoid meningioma, (b) Transitional meningioma, (c) Meningothelial meningioma.

4. Discussion

Meningioma cases occur mostly in the 41-50 years age group (45.7%), other sources say that meningiomas are more common in middle age. Meningioma data in Scandinavia mentions the incidence of meningioma at the age of 40-44 years, this was also conveyed by Al-Nuamiy who mentioned the incidence of meningioma in the 18-70 year age group with an average age of 46 years. In these three patients, the incidence rate of meningioma was following the stated mean age were in the first patient was 58 years old, the second patient was 46 years old and the third patient was 38 years old. Meningiomas occur mostly in women in the age group (41-50 years) due to one factor due to the use of oral contraceptives or other hormonal contraceptives for reasons of gynecological treatment or fertility problems consumed for 1-4 years [12, 13]. In these three patients, all three used hormonal contraceptives that lasted more than 4 years, namely in the first patient used for 10 years, the second patient used for 15 years, the third patient used for 12 years. In these three patients, the occurrence of meningiomas was likely associated with exogenous progesterone exposure.

The incidence of meningioma was also associated with the presence of a neurofibromatosis 2 (NF 2) gene mutation, in these three patients clinically and physical examination did not find any signs that led to neurofibromatosis 2 symptoms, namely no hearing loss, balance disturbance, or brown spots such as coffee color on the skin (café au lait spot). The location of the meningioma often in the supratentorial area about 85-90%, this also happened in these three patients, the location of the occurrence of meningiomas based on the results of head CT scan with contrast in these patients was supratentorial. The first patient the location of the meningioma was in the frontal, temporal, temporo-basal and occipital lobes, in the second patient the location of the meningioma was in the frontal lobe, while in the third patient the sphenoid wing.
Clinical symptoms that appear vary depending on the location of the tumor, such as chronic progressive headaches and focal neurological deficits such as visual disturbances, diplopia, hemiparesis [2, 4]. In these three patients, clinical symptoms appear in the form of decreased consciousness, progressive chronic headache, and progressive hemiparesis. The treatment option for meningioma is resection. In these three patients, total tumor resection with Simpson grade IV classification for the first patient and Simpson grade II for the second and third patients, grade II Simpson showed a risk of recurrence of up to 19%. After resection, these three patients gave good results namely the patient regained consciousness and there was an improvement in his motor skills.

Hormonal Therapy, such as antiprogestosterone, for example, mifepristone can inhibit tumor cell growth [14]. In some studies it is said that hormonal therapy, namely antiprogestosterone is given to meningiomas that are not operated on, but there is no clear evidence that recommends antiprogestosterone treatment in recurrent and inoperable meningiomas [14, 15]. Thus, hormonal therapy was not recommended in these three patients. According to some sources, the highest incidence of meningiomas is in grade I meningiomas as much as 80-90% followed by 20-25% degree II [3].

From the immunohistochemical examination of these three patients, it was found that the progesterone receptor expression was > 90% in the tumor cell nucleus. Positive progesterone receptor expression is a marker of good prognostic value and a reduced risk of recurrence. Fakhrjou stated that progesterone plays a role in tumorigenesis or the development of meningiomas. If the expression of progesterone receptors is negative in meningiomas, it indicates the biological behavior of tumor cells and is associated with abnormalities on chromosomes 14 and 22 de novo so that it increases the potential for the aggressiveness of tumor cells, as well as the risk of recurrence [11]. Meningiomas that express negative progesterone receptors have high mitosis and angiogenesis tumor cells are more aggressive and tend to recur. A positive progesterone receptor is associated with a better prognosis [10].

5. Conclusion
In the case series of the three meningioma patients with a history of using hormonal contraceptives for more than 4 years in all three and having performed a resection, the results of immunohistochemical examinations showed progesterone receptor expression > 90% in tumor cell nuclei.

Compliance with ethical standards

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Disclosure of conflict of interest
This case report doesn't have a conflict of interest.

Statement of ethical approval
This case report has been accepted by the patient and the patient has been signed an informed consent form for the anonymous publication of medical data.

Statement of informed consent
Informed consent was obtained from all individual participants included in the study.

References


