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Review

Meningioma and Its Treatment: An Update

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ABSTRACT

Meningiomas are benign tumors that are found in the cerebral cortex. They pose a risk and can result in death. Technically, the brain falls into the category of tumors, but as it grows, it puts pressure on the brain. Interestingly, meningiomas containing progesterone receptors are therefore more prevalent in women. It has been observed that meningiomas have three stages tumor location, tumor shape, degree of spread, and relapse rate. Meningitis and its treatment are being researched more as technology advances with the current therapy. The review includes the pathophysiology of meningitis, molecular mechanisms, diagnostics, and therapeutic options.

Keywords: Brain tumor, meningioma, meningitis, pathology

Central nervous system (CNS) tumors are a heterogeneous neoplasm group with an important morbidity and mortality rate.[1] Since it causes symptoms in the case of pressure, it can often be late to detect. Symptoms of diagnosis may vary depending on the tumor's growth rate, CNS location, and the age of the individual.[2]

Meningiomas, a CNS tumor, are the most common intracranial tumors that originate from the arachnoid cells of the leptomeninges and are more common than other tumors.[3] Meningiomas, benign tumors of CNS tumors, represent 13-26% of intracranial tumors.[4] For the development of meningiomas, there are two opposing main hypotheses. The first is that, while supporting the independent evolution of these tumors, the other suggests, by contrast, the spread of an unprecedented clone transformation of tumor cells through cerebral spinal fluid. In the formation of meningiomas, the neurofibromin 2 (NF2) gene is an important internal risk factor and some exogenous risk factors are suspected, but only exposure to ionizing radiation has been proven.[5]

The World Health Organization (WHO) classifies meningiomas as grade I, grade II, and grade III in its system, depending on various histological characteristics.[6] Although meningiomas are known as benign tumors, they are up to 15% atypical and up to 2% anaplastic according to WHO 2016 histological criteria. Treatments for primary care are observation, surgery, or radiotherapy, but surgery and radiotherapy are recommended together in grade II and grade III tumors.[7]

EPIDEMIOLOGY AND ETIOLOGY

Meningiomas are rare in children and their incidence increases with age. The incidence was higher in women than in men.[8,9] Based on data from the Central Brain Tumor Registry of the United States (CBTRUS) from 2004 to 2006, the age-adjusted incident rate (per 100,000 people) was 8.44 for women and 3.76 for men.[10] Overall, meningiomas account for more than a third of primary CNS tumors, with an incidence rate of 8.03 per 100,000 population. This makes them the most common primary intracranial neoplasm.[3,11]

In recent years, there has been an increase in the incidence of primary brain tumors in general and especially meningitis.[12] Etiological factors such as head trauma, ionizing radiation, hormones, and

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other receptor binding regions, genetic factors, and viruses were identified as factors in the formation of meningitis.[8]

Among these factors, people with certain mutations of NF2 in the neurofibromatosis gene contain a very significant risk for meningitis. Since women are twice as likely as men to develop meningitis and these tumors contain hormone receptors, both endogenous and exogenous hormones are assumed to have an etiological role.[13]

MOLECULAR GENETICS OF MENINGIOMAS

Meningiomas make up a third of tumors in the nervous system. Unlike other types of cancer, it has three stages. These are classified as grade I, grade II, and grade III. According to WHO data, 80% of meningioma patients are grade I and can be treated with surgical resection.[14] WHO 2016 tumor classification has taken a histological-molecular attitude by adding molecular data to the classification to identify primary brain tumors. Despite this, the classification of meningiomas continues to be based entirely on histopathological characteristics. However, recently, with the use of next-generation sequencing techniques, the idea emerged that molecular mutations are also effective in meningiomas.

Mutations in meningiomas can be divided into non-NF2 and non-NF2-based changes.[15] The NF2 mutation is a gene that causes tumor-causing disease. It has an incidence of one in 25,000 and has a dominant hereditary property. The NF2 gene is most often involved in the production of meningitis tumors. The NF2 mutation has consequences such as frameshift, non-functioning protein array productions, and 22q chromosome loss. In particular, the loss of 22q has an important role in the development of meningitis.[15,16]

Some of the other genes involved in the formation of mutation-induced meningitis include TNF receptor-associated factor 7 (TRAF7), v-akt murine thymoma viral oncogene homolog 1 (AKT1), Kruppel-like factor 4 (KLF4), smoothened (SMO), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA). According to the results of the most effective mutation research, 55% NF2, 20% TRAF7, 9% AKT1, 9% KLF4, 4.5% PIK3CA, and 3% SMO mutations were found to be effective in meningitis formation. It was observed that about 80% of general meningitis cases were caused by genetic mutations.[17]

PATHOLOGY

When the pathological aspect of meningiomas was examined, nine histological subunits of the grade I stage were identified. These are meningothelial, fibrous, transitive, psammomatous, angiomatous, microcystic, secretion, rich, and metaplastic meningiomas by lymphoplasmacytic. In grade II, chordoid is divided into histological subunits as cell and atypical meningiomas, and in grade III as papillary, rhabdoid, and anaplastic meningiomas.[18] Grade II and grade III meningiomas are less common than grade I meningiomas. Histological relapse rates were 7-25% in phase 1, 29-52% in grade II, and 50-94% in the grade III phase.[19] Embolization of some meningioma sub-branches is requested before surgery. In the pathological examination of such embolized meningiomas, microscopic necrosis chambers were detected in 40-89%. In non-embolized meningiomas, the rate is 16%.[20] Peritumoral brain edema (PTBE) can be seen in the types of secretory or angiomatous meningitis. It was observed that the vascular endothelial growth factor was slightly effective in the formation of PTBE.[21] At the same time, mast cells, hypoxia-inducible factor-1 (HIF-1), aquaporin 4-5, and interleukin 6 (IL-6) factors also play a role in the formation of PTBE alone or together.[18,22] Sometimes meningiomas may show malignant tumor characteristics as a result of histological progeny.[23] Approximately 28% of meningioma patients undergo maligned histological progression. Maintaining telomere length plays an active role in the progression of malignant tumors. Telomerase reverse transcriptase (TERT) mutations have an effect on patients undergoing malignant histological prosthesis. TERT mutations are important genetic changes that play a role in the progression of meningiomas.[24] Although meningiomas grow slowly, the TERT mutation activates their growth and accelerates their spread. It also causes a significant increase in the rate of relapse of the disease. In the study of meningioma patients, the TERT mutation was associated with mRNA expression. TERT mutations are thought to have further therapeutic consequences. [25]

DIAGNOSIS AND TREATMENT

The appearance of meningiomas is generally not specific, but the location and compression of the neighboring brain and vascular structures can lead to focal neurological deficits (including cranial nerve deficits).[26] Although most meningiomas are asymptomatic, patients usually experience only mild headaches in the early stages. When tumors progress,

numerous complications and poor functional outcomes occur.[27] Common symptoms in patients are: headache (33.3-36.7%), focal cranial nerve deficiency (28.8-31.3%), seizures (16.9-24.6%), cognitive change (14.4%), weakness (11.1%), vertigo/dizziness (9.8%), ataxia/gait change (6.3%), pain/sensory change (5.6%), proptosis (2.1%), syncope (1.0%) and asymptomatic (9.4%). In the fate of these symptoms, the initial definitive diagnosis of meningitis can be made via magnetic resonance imaging (MRI) or contrast computed tomography (CT).[26,27] Pet-based imaging using Somatostatin receptors (SSTRs) ligands such as DOTA-(Tyr3)-octreotate (^{68}Ga-DOTATOC) and 68 is cited as an auxiliary additional diagnostic tool for meningioma cells somatostatin-receptor subtype 2 (SSTR2).[28] As with any type of tumor, surgery is the first treatment method in meningitis. The location of the tumor, brain tissue invasion and vascular condition limit surgical operation. A patch is used to prevent recurrence after tumor removal.[29] The extension of the area where the tumor is removed is measured by Simpson rating and classified at five degrees. Relapse rates occurring within five years of tumor removal are 7-23% for type 1, 50-55% for type 2, and 72-78% for type 3.[3] However, neurological neurocognition and functional results may occur in these patients that reduce the quality of life after surgical operation. At this stage, the location of the tumor is very important. In order to completely clean the area where the tumor is, it is necessary to remove the bone it is clinging to. Advances in neurosurgery are a hope that the quality of life of patients will not decrease. Among these developments, high-resolution exoscope systems enable wide focus and quality video images. They are especially useful in the treatment of spinal meningiomas.[30]

Radiotherapy is the second type of treatment for meningiomas that cannot be treated with surgical intervention. Although it is not as effective as surgical intervention, it is used to control local growth. Radiotherapy methods are performed in two types: external beam radiation therapy (EBRT) and single fraction stereotactic radiosurgery (SRS). The SRS is used for meningiomas smaller than 30 mm in diameter. Prevents edema and necrosis complications. EBRT method is used especially in the treatment of meningitis, which is inhabited in the brain. EBTR prevents local relapse and provides a wider radiation field.[31] Radiotherapy performed after surgery is called adjuvant radiotherapy. The aim of adjuvant therapy is to reduce the risk of postoperative relapse and to improve it in a controlled manner. Adjuvant therapy has been shown to be particularly effective in grade I meningiomas. It is mostly used to treat those located in high-risk location areas and tumor areas that have not been fully cleaned.[32] If we examine the evolution of radiotherapy in the treatment of meningioma, improvements in 3D conformal radiation therapy (3D-CRT) and multi-leaf choline, which first appeared in the early 1990s, have been applied. In the following years, EBRT and SRS methods, which are still used today, started to be used. Intensity-modulated radiation therapy (IMRT) is performed by the EBRT method. The purpose of this treatment is to scan the entire region by providing the desired dose to the patient. Finally, particle treatments are included. This method, which is very popular worldwide in current times, is done with carbon or proton ion therapy. The aim of particle treatment is to reduce the rate of exposure of neighboring tissues and cells and to break down even long-lasting tumors. However, this method is still under investigation. In the research, especially meningitis around the pituitary gland was seen to have good effects.[33]

Another treatment method is systematic treatments, which are largely experimental. It is preferred in cases with high meningiomas and relapse rates in areas that are difficult to treat surgically.[34] Chemotherapy is the first of the systematic treatments. Trabectedin, a chemotherapeutic agent, interacts with meningitis transcriptionally. In this way, it is an important agent for treatment and studies are continuing. Secondly, molecular therapies are discussed. Tumor-targeted molecular therapies are developed and continue to be developed by identifying specific genetic differences in meningiomas. PIK3CA, AKT, and mTOR pathways are used in molecular therapy. Another treatment method that is still in the research phase is immunotherapy. Maling meningiomas in the immunosuppressive microenvironment were found to respond to treatment. In this way, it is investigated whether it is possible to treat recurrence by inhibiting the checkpoints of high-grade meningiomas. These methods have also given hope to patients with other types of cancer.[28,31,35]

In conclusion, benign tumors that originate from the meninges, a membranous layer that surround the central nervous system and spinal cord, are called meningiomas. It is usually more common in women than its appearance in adults. Due to their benign structure, they cannot metastasize and their structure is low statistically, one in 1,000 people is diagnosed every year. Although it is not known for certain why meningitis occurs, it is known that it is triggered by

causes such as head trauma, genetic predispositions, excessive radiation victimization, and genetic mutations are especially thought to be effective. Symptoms of meningitis are usually asymptomatic and appear in a brain MRI taken incidentally. The best diagnostic method is contrasted MRI imaging. Follow-up is an option in asymptomatic patients with an incidental diagnosis. Surgery is preferred as the initial step in the treatment of symptomatic individuals. It is aimed to reduce the risk of relapse by removing the entire tumor with surgery. The grade stage of the tumor removed by surgical intervention is determined by pathological examination. In cases where surgery is risky, radiotherapy is preferred as the second option in treatment, radiosurgery is often performed. As a result of the developments in modern medicine, systematic treatments have also come into play. It is hoped that advances in medicine and genetics will allow us to treat meningitis at the molecular level and decrease the incidence of recurrence in the coming years.

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