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Pathophysiology

CLINICAL PRESENTATION, PATHOPHYSIOLOGY, AND TREATMENT OPTIONS

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ABSTRACT Meningioma is the most common type of non-glial intracranial neoplasm (Rogers et al, 2015). They originate in the meninges, which consist of the outer three layers of tissue between the skull and the brain, covering and protecting the brain; specifically, it is in the middle meninge layer – the arachnoid – where these tumors originally form (Mayo Clinic Staff, 2020). They may compress or squeeze the adjacent brain, nerves, and vessels, leading to symptoms such as headaches, vision or hearing changes, memory loss, or weakness; however, symptoms usually appear gradually, as it can take years for these tumors to grow (Mayo Clinic Staff, 2020). Even though they may occur at any age, they are mostly discovered in older patients. The condition is also twice as likely to be diagnosed in women.

This paper will review meningiomas and their classifications, examining clinical presentation, epidemiology, and pathophysiology. It is crucial to determine this tumor's staging and grading, including clinical guidelines for diagnosis and early management; diagnostic tools must also be examined, so practitioners are aware of current technologies that are used in the field of neurological oncology. By reviewing the most recent evidence-based research, effective treatment options available for meningiomas can also be identified and further explored. These interventions include not only traditional approaches such as radiation therapy and surgery, but also chemotherapy options that are currently being studied. Management strategies may be combined to offer patients a comprehensive treatment approach for this condition, improving patient outcomes.

KEYWORDS :

Epidemiology and Etiology

Meningiomas are almost always benign. However, because their intercranial location can cause adverse symptoms in patients, the condition can be fatal. They are most frequently diagnosed primary brain tumor (Wiemels et al., 2010). According to the Central Brain Tumor Registry of the United States (CBTRUS), between 2010 and 2014, meningiomas accounted for 36.8% of all primary brain and central nervous system (CNS) tumors, with an annual incidence of 8.14 per 100,000 population (Ostrom et al., 2017). This is the highest incidence rate of any tumors. Furthermore, the prevalence of meningioma that has been confirmed pathologically is estimated at 97.5 per 100,000, with over 170,000 individuals currently diagnosed (Ostrom et al., 2017). These patients usually have one meningioma, as only 10% have multiple tumors (Fung, 2014). In females, the incidence rate of meninges tumors is roughly 11.26/100,000 population, which is more than double than that for males (5.15/100,000) (Ostrom et al., 2017). These tumors are also more frequently found during older adulthood, with the condition peaking in the sixth decade of life (Louis et al., 2016).

Risk Factors

The etiology of meningiomas is not clear. However, it is known that meningioma cells are similar in appearance to arachnoid cap cells, which are thought to be where the tumor cells originate (Wiemels et al., 2010). Patients may have inherited susceptibility to meningiomas, such as those with a family history or certain mutations in the neurofibromatosis gene (*NF2*); those with mutations in this gene are more likely to have multiple meningiomas, as it is a tumor suppressor (Wiemels et al., 2010). A unique cytogenetic alteration is monosomy 22; mutations (or deletion) of the *NF2* gene – which is located on chromosome 22q12 – are present in roughly 50% to 80% of sporadic meningiomas (Zang et al., 2001). *NF2* gene encodes for a protein called merlin (i.e., schwannomin), which helps to regulate tumor formation and cell proliferation in meningiomas; merlin links the plasma membrane proteins to actin cytoskeleton, inhibiting the excessive spread of cells (Shaikh et al., 2018). Those with *NF2* mutations have a reduced merlin levels, resulting in increased YAP expression and cell proliferation (Shaikh et al., 2018).

Another risk factor is exposure to high-dose ionizing radiation, although lower doses may also increase risk (Fung, 2014). This is the primary environmental variable associated with meningiomas. Furthermore, since women are at a significantly increased risk for this type of tumor, there may be an etiologic role for endogenous and exogenous hormones (Wiemels et al., 2010). There is recent evidence showing the rapid growth of meningiomas in pregnant women (Baxter et al., 2009). This may indicate that hormonal contraceptives' widespread use contributes to their tumorigenesis; 88% of meningioma tumors that are excised during surgical interventions test positive for progesterone receptors, while 40% have estrogen receptors and 39% show evidence of androgen receptors (Fung, 2014). These receptors are significantly more likely to be found in Grade I meningiomas (Korhonen et al., 2006).

Diagnosis

Clinical Presentation

There are no pathognomonic presentations for this condition. However, clinical symptoms may include headache from rising intracranial pressure as well as focal neurological deficits, including cranial nerve; patients may also present with generalized or partial seizures caused by focal mass effect (Buerki et al., 2018). Some exhibit personality changes and/or altered levels of consciousness, especially in anterior or parasagittal meningiomas (Buerki et al., 2018). Unfortunately, these may be misdiagnosed as dementia or depression. Some patients may also display nausea, vomiting, drowsiness and/or muscle weakness, with changes in vision and hearing; however, these tumors may also be asymptomatic, with detection only after a brain scan for isolated symptoms (Traylor & Kuo, 2020).

Pathophysiology and Types

There are numerous types of meningiomas, depending on where they are found in the brain. According to the American Neurological Association of Surgeons (ANAS), some tumors grow along the dural lining in the venous sinuses, where there is an abundance of arachnoid cap cells (Traylor & Kuo, 2020). Those that develop on the brain's surface (underneath the skull) are known as convexity meningiomas, while skull base meningiomas grow in the bones at the skull's bottom; parasagittal and falcine meningiomas develop in the tissue layer separating the brain's two sides, while those hat grow inside the ventricular system (where production of cerebrospinal fluid occurs) are categorized as intraventricular meningiomas (Traylor & Kuo, 2020). There are many others, such as those that grow near the optic nerve, olfactory bulb, spinal cord, or underside of the brain.

These tumors are classified according to the World Health Organization (WHO) tumor grading, which recognizes 15 meningioma histological subtypes based on their microscopic cellular characteristics; the identifying features are spherical formations of meningothelial cells (i.e., whorls), which mineralize into psammoma bodies, as well as central chromatin clearing and intranuclear cytoplasmic pseudoinclusions (Buerki et al., 2018). Epithelial membrane antigen is the immunohistochemical marker used to

identify a meningioma (Buerki et al., 2018). These tumors are organized into three grades which not only indicate the likelihood of recurrence, but particularly the rate of growth; this is based on cytological features (Louis et al., 2016). Grade I (benign) tumors grow slowly, with classifications such as fibrous, transitional, secretory, and metaplastic, while Grade II (atypical) tumors include chordoid and clear cell; finally, Grade III (malignant) tumors are also known as anaplastic meningiomas, and they can grow and spread rapidly (Louis et al., 2016).

Atypical meningiomas are diagnosed if there are three of the five histological features: 1) spontaneous intratumoral micronecrosis; 2) patternless sheet-like growth of tumor cells, with loss of whorling or fascicular architecture; 3) prominent nucleoli that are readily visible; 4) high cellularity; and 5) small cells with scant cytoplasm relative to nuclear size (Louis et al., 2016; Buerki et al., 2018). Grade II tumors have either 4^{+} mitoses per ten consecutive high-power fields or brain invasion, which is when the meningioma pushes past the connective tissue into the underlying cortex (Louis et al., 2016). These account for approximately 18% of all meningiomas and have a much higher likelihood of recurrence compared to Grade I tumors; finally, Grade III tumors meet most or all of the histological features, although the only requirement for classification is 20^{+} mitoses per ten consecutive high-power fields (Louis et al., 2016).

Diagnostic Tools

On CT scans, most meningiomas are hyperdense, with roughly a quarter demonstrating psammomatous calcifications; they may also invade the cranial vault, resulting in characteristic hyperostosis (Fung, 2014). However, recent guidelines for the meningioma diagnosis and treatment have been released by the European Association of Neurooncology (EANO), which explain that the most sensitive method for detection is contrast-enhanced MRI (Goldbrunner et al., 2016). Meningioma tumors are attached to the dura matter and appear as broad-based dural hemispheric or oval lesions; they present as isointense to the cortex on T1- and T2-weighted sequences, with a "CSF crest" visualized around the tumor (Goldbrunner et al., 2016). Tumors enhance strongly and homogeneously, with an estimated 50% of patients displaying an area of dural enhancement (i.e., "dural tail") (Fung, 2014). MRIs may be used during surgery to guide biopsies, while magnetic resonance spectroscopy (MRS) examines the tumor's chemical profile, determining its nature (Traylor & Kuo, 2020). However, definitive diagnosis may be difficult, requiring a biopsy (i.e., tissue sample) of the tumor; a neuropathologist can then identify the tumor's grade as well as if it is malignant or benign (Traylor & Kuo, 2020).

Treatment Options

There are traditional treatment options that patients with meningiomas may seek such as radiation treatment and surgery; chemotherapy is rarely unless there are no alternatives. Surgery is a common management approach and usually the preferred intervention in tumors with defined borders, as this allows for complete surgical removal (Traylor & Kuo, 2020). However, perhaps the most important consideration in managing this condition is predicting the risk of recurrence; both tumor location and extent of resection are predictive of recurrence, as well as certain tumor characteristics: 1) lacking calcification, 2) vascular endothelial growth factor (VEGF) expression, and/or 3) monoclonal antibody tumor proliferation markers (Shaikh et al., 2018). Furthermore, males are more likely to experience recurrence. In patients with a low chance of recurrence as well as mild (or no) symptoms, observation may be recommended; this may also be the preferred course of action in older patients with slow growing tumors, for whom the risks of surgery outweigh the benefits (Traylor & Kuo, 2020).

Radiation Therapy

Radiation therapy (RT) is the first-line treatment for tumors that cannot be surgically resected; RT may also be used in postresection as an adjuvant therapy (Buerki et al., 2018). There are two primary types of RT employed: fractionated external beam RT (EBRT) and single-fraction stereotactic radiation (SRT); EBRT delivers tightly targeted radiation beams to the tumor, while SRT uses a higher dose of ionizing radiation (Kirkpatrick et al., 2017). While EBRT requires several sessions, there is usually only one in SRT; however, SRT is limited to smaller tumors that are less than 30 mm in diameter, as well as those not directly adjacent to structures that may be sensitive to radiation (Kirkpatrick et al., 2017). Grade I tumors are irradiated with a lower dose (50 Gy), while Grade II–III tumors necessitate higher doses (60 Gy) with daily fractions over five to six weeks using EBRT; focal alopecia and fatigue are acute toxicities resulting from EBRT, which do not normally occur when employing SRT (Kirkpatrick et al., 2017). Even though RT has shown success in managing meningiomas, it is not as effective as surgery at relieving tumor-related neurological symptoms (Kirkpatrick et al., 2017).

Surgery

In symptomatic meningiomas, surgery with the goal of gross total resection (GTR) is the preferred treatment (Shaikh et al., 2018). For progression-free survival (PFS), the estimated 10-year rate is roughly 60% to 80% when using GTR in Grade I meningiomas and 50% for those with subtotal resection (STR); the risk of recurrence in patients who receive STR is 50% at five years, so adjuvant radiation may be considered (Shaikh et al., 2018). However, even though STR is considered non-invasive when compared with surgery, there are potential risks, including toxicities and cranial neuropathies from RT-induced injury (Shaikh et al., 2018). Stereotactic radiosurgery (SRS) – which uses radiation as with SRT – is also a recommended therapy, especially in those who may present with surgical difficulties; these include the patient's age and any comorbidities, the tumor's location and recurrence, as well as risks for neurologic morbidity (Cohen-Inbar et al., 2016).

For Grade II meningiomas, initial management involves surgery, aiming for maximal safe resection. With patients receiving GTR, the five-year PFS rate is 60% to 90%, while for those who receive STR, it is only 30% to 70% (Sun et al., 2015); at 10 years, the PFS for GTR has been shown to be as high as 87%, but only 17% for STR (Goyal et al., 2000). An accepted management approach is to utilize post-operative EBRT after STR, which has an estimated five-year PFS ranging from 40% to 90% (Sun et al., 2015). SRT may be used instead of EBRT, although it is usually more beneficial for tumors that are smaller in size (Cohen-Inbar et al., 2016). For Grade III meningiomas, surgery – with the goal of maximal safe resection – is the preferred course for most patients (Shaikh et al., 2018). Using GTR, the five-year PFS rate is 28%, while the rate after STR is negligible; however, studies show that adjuvant RT can improve PFS compared with surgery alone (Zhao et al., 2015). Post-operative EBRT should be performed after any resection, no matter the extent (Shaikh et al., 2018).

Chemotherapy

There chemotherapy options for meningiomas are limited. According to National Comprehensive Cancer Network (NCCN) guidelines, somatostatin receptor agonists, alpha interferon, and VEGF inhibitors are the only classes of recommended drugs for treating these tumors (Kaley et al., 2015; Chamberlain et al., 2008). Bevacizumab, an anti-angiogenic VEGF inhibitor, can be used as a monotherapy for recurrent meningiomas; its efficacy has been studied in combination with octreotide (somastatin analogue) and everolimus (mTOR inhibitor) in recurrent Stage I–III meningiomas (Paldor et al., 2016). Results indicated acceptable and manageable toxicity, with six-month PFS at nearly 60%; additionally, growth rates were decreased by more than 50% in some patients (Paldor et al., 2016).

CONCLUSION

Meningiomas are intracranial tumors originating in the meninges; patients may present with symptoms such as headaches or vision/auditory changes, although they gradually appear –some patients are asymptomatic, which may be due to tumors' slow growth. There are risk factors for meningiomas, including *NF2* gene mutation, high-dose ionizing radiation, and excess hormones; women are twice as likely as men to be diagnosed, with increasing incidence rates as people age. Based on WHO tumor grading, there are numerous meningioma histological subtypes, with Grades I-III (benign, atypical, and malignant, respectively). Although CTs can be useful in diagnosing this condition, MRIs are the gold standard; they can be used to guide biopsies, which are the only tool that can definitively diagnose and grade a tumor.

There are three primary treatment modalities for meningiomas: radiation, surgery, and chemotherapy (although this is infrequently used). The deciding factor on what intervention to employ is the patient's risk of recurrence; for example, observation may be warranted in cases of slow growing tumors, depending upon the benefit-risk ratio. RT includes EBRT and SRT, which both have their uses in radiating tumors; the radiation dose depends on the Grade and location. However, there are risks for acute toxicities. Surgery is the

first-line treatment when there are symptoms associated with meningiomas; the goal is to safely resect as much of the tumor as possible. GTR is preferred, resulting in increased PFS rates, although there are times when only STR is feasible. Many patients follow surgery with some form of radiation as an adjunctive intervention, improving outcomes and reducing risks for recurrence. Chemotherapy is a last option, as studies show limited success in treating this condition. Nonetheless, current research is being conducted on novel medications and chemotherapy drugs; their evidence may prove useful for managing meningiomas in the future.

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