World Journal of Engineering Research and Technology
WJERT
www.wjert.org
SJIF Impact Factor: 5.924

MALIGNANT MENINGIOMA WITH EXTRA-CRANIAL METASTASIS: A CASE REPORT AND REVIEW OF LITERATURE

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Article Received on 19/08/2020 **Article Revised on 09/09/2020** **Article Accepted on 29/09/2020**

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ABSTRACT

Extracerebral metastasis can be present in patients with atypical or anaplastic meningiomas. On multivariate analysis, histological grade, Mitotic rate/HPF, Nuclear Atypia, Ki-67 (MIB-1 labelling index)and extent of resection remains important prognostic factors. The median survival for anaplastic meningioma remains 18 months, with 5-year mortality of 68%.

KEYWORDS: Atypical Meningioma, Extra Cranial Metastasis, Cervical Nodes.

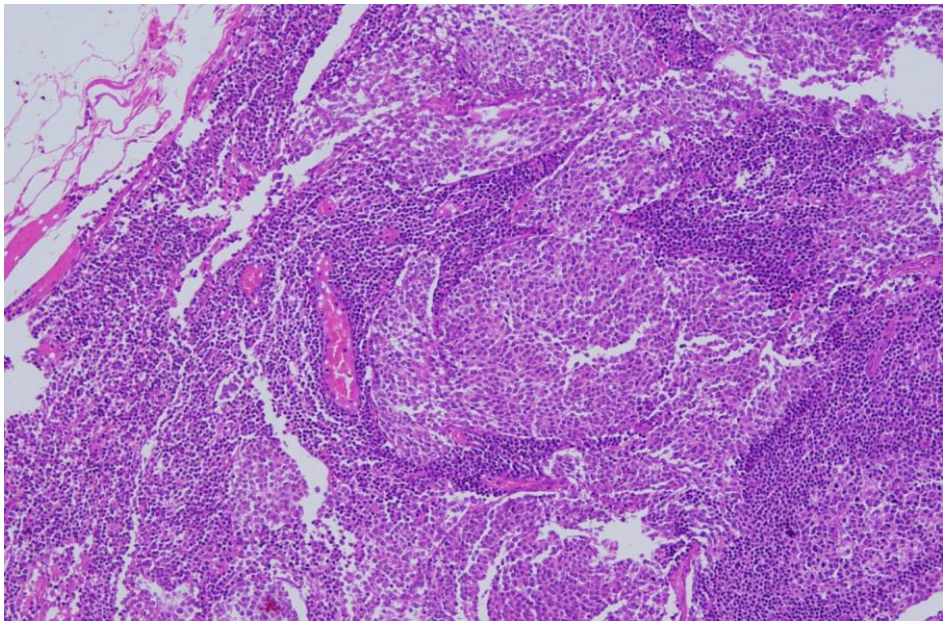
CASE HISTORY

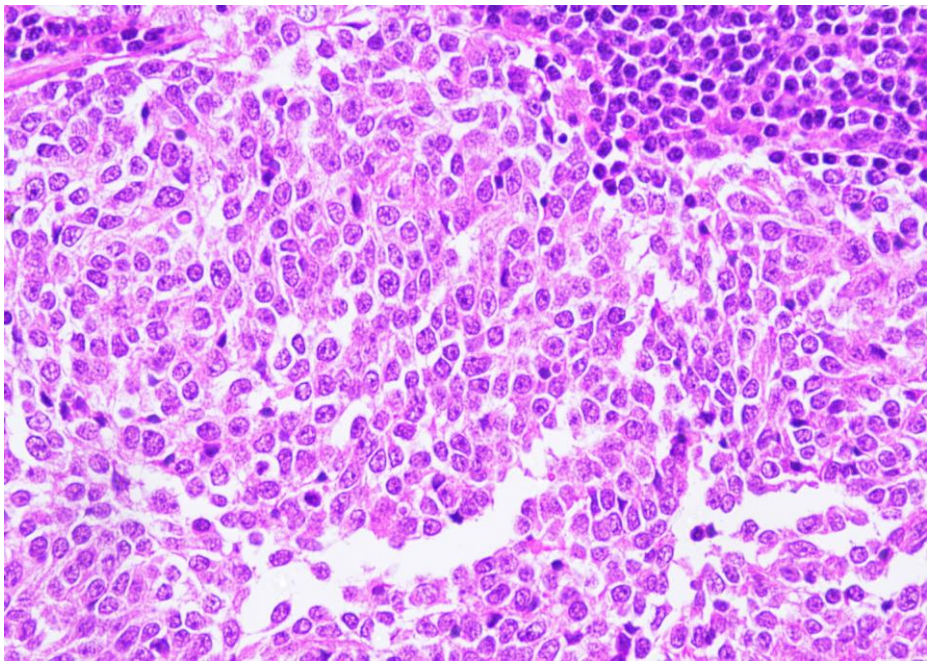
37-year-old male patient presented with headache, recurrent vomiting and giddiness of 2 months duration. On asking he admitted in having difficulty in walking in narrow corridor and change in hand writing. On examination he was conscious, alert with power of 5/5 in all four limbs. Eom- normal, left finger nose impaired with sways to left side. Left dysdiodocho kinesia was present and Planters- flexor.

CEMRI showed left cerebellar tumor with hydrocephalus. On craniotomy tumor was greyish pink in color, soft well defined, vascular and extra axial, vascular extra axial in posterior cranial fossa adherent to tentorium and falx cerebelli left sub-occipital craniotomy with simpsons grade 3 excisions of left tentorial meningioma was done.

HPE was reported as atypical meningioma with 15mitosis/10 High power field. No necrosis seen. MIB-1 labelling index of 40%.Tumor was negative for EMA, vimentin, CD45, synaptophysin. Adjuvant radiotherapy of 50GY in 25# was given with temozolomide.

A year later patient presented with a neck node in left posterior triangle. FNAC of neck node revealed metastatic small round cells suggestive of metastatic atypical meningioma. CEMRI of brain did not show any recurrence of disease. PET-CT SCAN showed FDG avid lymph nodes in left neck level III and IV. Left modified neck dissection was done, 9/39 neck nodes showed evidence of metastatic atypical meningioma cells with no peri -nodal spread. Adjuvant radiotherapy was given to neck.(Fig 1,2).





Four months later he presented with acute paraplegia and loss of bowel/ bladder control .B/L lower limb power -0/5.DTR B/L ankle / knee exaggerated B/L hypoaesthesia below L1.Planters B/L extensors. No cerebellar signs. MRI showed intradural extramedullary tumor of D11. Complete D11 with partial D10 and D12 laminectomy with tumor decompression was done. HEP confirmed presence of metastatic meningioma Ki67- 70-80%. Patient remained disease free for 15 months.

DISCUSSION

Meningioma is a slow-growing benign intracranial neoplasm arising from the arachnoid cap and with incidence of 14-19%.Meningioma is composed of neoplastic meningothelial (arachnoidal) cell. Local recurrence and recurrence along cranio-axial axis is well documented. Extracranial metastases from meningiomas are exceedingly uncommon and are usually found in <0.1-02 % of cases.[1,2] Rarely, delayed metastases may be seen several decades after treatment of the initial tumor and in the absence of local intracranial recurrence. The high recurrence rate noted for brain-invasive lesion is because of microscopic residual tumor tissue within the brain parenchyma or invasion of bone and dura that is not resected because of potential morbidity. Approximately 1% to 2.8% are considered to be anaplastic meningiomas. These develop more commonly in men, grow rapidly, recur within a short period after resection and metastasize distally even to sites other than the nervous system. Atypical meningiomas have been reported to occur after cranial irradiation for other tumors. These are usually found in younger patients (children undergoing cranial radiation for medulloblastomas, astrocytomas, leukemia and lymphoma). Radiation-induced meningiomas are more aggressive and can recur early after excision. They can also involve bone to a greater degree, preventing complete resection.[10] Benign meningiomas (grade 1) meningiomas have a low recurrence rate of 29-40% while anaplastic meningioma are aggressive and have a high recurrence rate of 50-78%.[8] Extracraninal metastases of meningiomas occurs in the lungs (60%), abdomen and liver (34%), cervical lymph nodes (18%), long bones, pelvis, and skull (11%), pleura (9%), vertebrae (7%), and mediastinum (5%). The various routes of dissemination are 1) Hematogenous dissemination via the jugular vein which may be responsible for metastasis in the cervical lymph nodes, cervical soft tissue, parotid gland, thyroid gland, cervical bones and lung/pleura. 2) The paravertebral venous plexus may be the primary route of metastases detected in the vertebrae, kidney, peri-renal tissue, and adrenal gland. 3) Lymphogeneous 4) cerebrospinal fluid (CSF) may also be implicated in the spread of meningioma.[9]

Perry et al.[3] reported 5 years mortality rate of 83% and median survival duration was 1.4 years in brain invasive meningioma. It has been found that up to 2% of all benign meningioma transform into malignant meningioma whereas up to 28% of all recurrent benign meningioma will be either atypical or anaplastic in nature.[4,5]

Perry et al.[6] additionally reviewed pathology slides of 35 patients at recurrence of meningioma. In 29 patients the grade of meningioma was in concordance with earlier grade, two reports were reported atypical from benign, and four were classified as benign which were initially reported atypical. Another review of 936 patients by jaaskelaninen et al.[7] revealed that 70 meningioma that were initially diagnosed benign at first presentation, 60 recurrent tumors remained benign but 10 tumors subsequently showed atypical or anaplastic changes. Other authors have also reported malignant progression with recurrence.

Genetic predisposition in Meningioma

In 1997, weber et al.[11] analyzed the genomic alterations in meningiomas. Using the World Health organization (WHO) criteria, this group of investigators classified meningiomas into benign (Grade I), atypical (Grade II), or anaplastic (Grade III). They determined a stepwise change in the genetic characteristic of benign tumors, as these become anaplastic. The loss on 22q, a gain on 1q, 9q, 12q, 15q, 17q, and 20 and a loss on 1p, 6q, 10, 14q and 18q resulted in an atypical meningioma. Further mutation with amplification on 17q and al loss on 9p (the CDKN2A, CDKN2B, and ARF genes) resulted in an anaplastic tumor,[12,13] The only specific abnormal known genes are the NF2 gene and the DCKN2A CDKN2B, and AFR genes (5, 61). Benign meningiomas are monoclonal and up to 70% can have the 22q12 mutation. With accumulation of more mutation, they can become atypical and progress to anaplastic type of meningioma.In meningioma, a fairly good correlation exists between histological grading and Ki-67 antigen expression as determined by immunoreactivity with the MIB-1 monoclonal antibody. Other markers may also aid in the segregation of benign versus potentially aggressive meningioma. Nagashima et al. investigated the expression of c-myc protein and messenger ribonucleic acid (mRNA).

Classification and Grading System

The world health organization (WHO) classifies meningiomas into three types as a risk assessment for the likelihood of recurrence and/or aggressive behavior: a) **B**enign (grade I) includes meningothelial, fibrous, transitional, psammomatous, and angioblastic cells. b) Atypical (grade II) includes chordoid, clear cell, and atypical cells) Anaplastic/Malignant

(grade III) includes papillary, rhabdoid, and anaplastic cells. Two studies from the mayo clinic reported by perry et al.[3,6] In one of the study,[6] the authors analyzed meningioma from 581 consecutively treated patients and provided grading recommendations based primarily on those cases. The histological features assessed included cellular pleomorphism, nuclear atypical, presence of macronuclei, mitoses, necrosis, maximal mitotic rate, level of cellularity, and brain invasion. Brain invasion, sheeting, absence of nuclear atypia or celluar pleomorphic. Mitotic rate of > 4 mitoses /10 high-power microscopic field (HPF) was univariately associated with decreased recurrence-free survival.

On multivariate analysis microscopic brain invasion emerged as the most powerful predictor of reduced recurrence-free survival. In their study, Perry et al.[14] focused on the significance of brain invasion and other indices of malignancy in meningioma by assessing 116 cases on the basis of histologically confirmed brain infiltration, extra cranial metastases, or frank morphological an aplasia (defined as having >20 mitotic figures /10 HPF or exhibiting a loss of meningothelial differentiation resulting in carcinoma, sarcoma, or melanoma-like histology).In his series only 17% of brain invasive meningioma exhibited frank anaplasia; 23% were benign and large majority were re-classified as atypical meningioma.

TABEL 1. Meningioma grading: The mayo Clinic scheme
Pathological criteria for the diagnosis of atypical meningiomas > 4 mitoses/10HPF (> 2.5/mm^2)
Or at least three of the following features;
Sheeting
Macronuclei
Small cell formation
Hypercellularity (.53 nuclei/HPF; > 118/$mm^{2)}$
brain invasion
pathological criteria for the diagnosis of anaplastic meningiomas
>20 mitotic figures/10 HPF(>12.5 mm^2)
Or
Focal or diffuse loss of meningothelial differentiation resulting in carcinoma, sarcoma, or melanoma-like appearance
HPF, high power microscopic fields (3, 6).

In 2000, the WHO modified earlier classification endorsing the proposed grading by Mayo clinic researchers.

TABLE 2. Meningiomas grouped by likelihood of recurrence and World health Organization classification	
Meningiomas with low risk of recurrence and aggressive growth	
Meningothelial meningioma	WHO Grade I
Fibrous (fibroblastic) meningioma	WHO Grade I
Transitional (mixed) meningioma	WHO Grade I
Psammomatous meningioma	WHO Grade I
Angiomatous meningioma	WHO Grade I
Microcystic meningioma	WHO Grade I
Secretory meningioma	WHO Grade I
Lymphoplasmacyte-rich meningioma	WHO Grade I
Metaplastic meningioma	WHO Grade I
Meningiomas with greater likelihood of recurrence and/or aggressive behavior	
Atypical meningioma	WHO Grade II
Clear cell meningioma (intracranial)	WHO Grade II
Chordoid meningioma	WHO Grade II
Rhabdoid meningioma	WHO Grade III
Palillary meningioma	WHO Grade III
Anaplastic meningioma	WHO Grade III
Meningiomas of any subtype or grade exhibiting high proliferation indices or brain Invasion	WHO Grade III
" WHO, World Health Organization	

Diagnosis/Imaging

It has been found that MRI or CECT scan cannot differentiate between benign meningioma and anaplastic meningioma. Several studies have shown that distinction between benign and anaplastic or atypical meningioma is not particularly reliable with magnetic resonance imaging (MRI). Recently, diffusion weighted (DW) imaging has been used to image primary brain tumors. It has been determined that the apparent diffusion coefficient (ADC) value could correlate with tumor cellularity and grade.[15]

There are, therefore no imaging to date to diagnose various grades of meningioma. Neither cerebral angiography nor positron emission tomography has reported to reveal any specific characteristics of atypical or anaplastic meningioma.

Prognostic factors

Extent of Resection

Excision should be as compete as possible to allow a possible cure. If required, a margin of Dura-mater and or bone should be excised around the tumor.

Brain Invasion

Cranial base lesions can be difficult to excise totally because of potential morbidity or technical problems. Meningioma that are densely adherent to the cortical surface may also be difficult to totally excise without significant morbidity. Such tumor often require adjuvant therapy and/ or repeat surgery at **recurrence.**

Pathological Factors

Cellular pleomorphic, nuclear Atypia, small cell cytology, Sheeting, Maximum Mitotic rate.

Molecular markers

Perry et al.[12] determined that the CDKN2A deletion, along with a 9p21 deletion, Elevated MIB -1 index is a predicator of malignant progression, worse survival rates, and increased recurrence. Other markers may aid in the segregation of benign versus potentially aggressive meningioma. Nagashima et al. investigated the expression of c-myc protein and messenger ribonucleic acid (mRNA).[15]

Treatment

Gross total removal of tumor remains the primary treatment.In case of involvement of dura or bone should be excised completely. Some Neuro-surgeons prefer to do Pre-operative Embolization of meningiomas with polyvinyl alcohol, alcohol, gelatin foam, coils/ micro coils, and Avitene (Davol, Inc., Cranston, RI), among other agents, has been used for several decades,[16] to minimizes blood loss, reduce tumor volume, and makes surgical excision easier.

Radiotherapy

Consensus favors administering EBRT early to patients who have undergone subtotal resection. However there are no prospective controlled studies supporting this.[16,17]

SRS has now become part of the armamentarium when treating atypical and anaplastic meningioma. It could probably be offered to the patients as soon as possible postoperatively for any residual tumor, along with EBRT to the tumor bed. SRS may not have any effect on infiltrative areas which are not appreciated during treatment planning.

Proton beam therapy has also been considered for primary and recurrent atypical and anaplastic meningioma. Proton beam therapy allows high dosages of radiation delivery to regions near critical structures. It also enables treatment of tumors with irregular shapes. Both hug et al.[18] and/ Noel et al.[19] Showed that a proton boost, combined with >60 Gy photon therapy, can improve survival and local control. Hug, etal and Noel et al.[18,19] reported a 5-years survival rate of 89% for atypical tumors and 51% for anaplastic tumors.

Chemotherapy

The combination of cyclophosphamide, Adriamycin and vincristine treatment was reported to be effective chemotherapy for a malignant meningioma that arose within the cranium.

However, no effective chemotherapy has so far been reported for anaplastic meningioma. There are currently no clear guidelines for the treatment of metastatic meningioma. Surgery and radiotherapy in combination are used. Prognosis is considered to be poor.

Platelet-derived growth factor (PDGF) subunits and their receptors; specifically PDGF-A PDGF-B, and PDGF-B receptor are expressed in meningioma .This growth factor and its receptor augments c-fos levels via an autocrine or paracrine loop causing cell division and tumor proliferation. At the moment, Gleevac (STI571), a PDGF antagonist, is being studied in a North American Brain Tumor Consortium phase one protocol.

Vascular endothelial growth factor (VEGF) and is receptor are expressed 10-fold in anaplastic meningiomas, and 2-fold in atypical meningioma compared with benign meningioma.[17] Peritumoral edema and micro vascular density correlate with VEGF expression). Therefore, anti- VEGF, anti-EGF, or anti-PDGF compounds may help to control tumor proliferation by an anti-antigenic property.

The latest systematic review revealed that adjuvant radiotherapy generally improves local control and OS in atypical and malignant meningiomas, although available data did not support this paradigm in the controversial subset of totally excised atypical meningioma.

CONCLUSIONS

A histological criterion for grade III meningioma is that it possesses malignant cytologic characteristics and resembles carcinoma sarcoma, or melanoma. Thus, differentiating these lesions from anaplastic meningioma is a challenge, especially in a lymph node. Based tumor, the aggressive growing pattern, and the immunohistochemistry profile, the diagnosis of metastatic meningioma was made in our patient.Atypical and anaplastic meningiomas are distinct entities whose prognosis remains poor. Surgery remains the main treatment .Subtotal resection has avery high recurrence rate Adjuvant treatment in form of EBRT, IMRT, SRS and brachytherapy therapy has been used with little success.

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