NOVEL DEVELOPMENTS AND NEW APPROACHES FOR DIAGNOSIS, CLASSIFICATION AND TREATMENT OF MENINGIOMAS:

A RETROSPECTIVE STUDY WITH ILLUSTRATION OF OWN DATA AND PRESENTATION OF CLINICAL COURSE, REVIEW OF THE LITERATURE WITH EVALUATION OF HISTOLOGY / HISTO-PATHOLOGY, PREDISPOSING - AND RISK - FACTORS, MOLECULAR - PATHOGENESIS AND GENETICS, RADIATION- & CHEMOTHERAPY AND DEMONSTRATION OF FUTURE PERSPECTIVES

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Abstract: **Meningiomas are the second most common central nervous system tumor, accounting for approximately 20 – 28 % of all primary adult intracranial tumors. The vast majority of meningiomas occur in patients between 50 and 60 years of age and are benign (WHO grade I), with a twofold higher incidence in women. The biological behavior of meningiomas is one of continued growth, ultimately leading to compression of neuronal structures. Uncommon benign meningioma subtype is secretory meningioma (SM), containing eosinophilic and periodic acid-schiff (PAS)-positive globular intracellular pseudopsamomas that are actually inclusions within intracytoplasmic lumina lined by microvilli. The inclusions and the surrounding cells, which might secrete and enclose the globules, were reported to have a positive immunoreactivity for cytokeratin (CK) and carcinoembryonic antigen (CEA). Immunohistochemistry staining of progesterone receptor (PR) for the tumor also showed mostly positive. SM was reported to account for 1.10 - 3.0% of all meningiomas. Female predominance, location preference, correlation with severe peritumoral brain edema (PTBE), and unique histopathological features had been reported. Histopathological examinations (with EMA, MIB-1 antibody and labeling index) of meningiomas give valuable prognostic information, although the methods are subject for interobserver variability. Tumor location, atypical or malignant histologic subtypes, and staining for the Ki-67 protein (MIB-1 antibody) with a high labeling index are the best predictors of tumor recurrence. Atypical (WHO grade II) and anaplastic meningiomas (WHO grade III) have a poorer prognosis than benign meningiomas. Fortunately, histologically atypical or malignant tumors comprise less than 10% of meningiomas. These two types of tumors are especially disposed to recurrence. The genetic alterations in atypical meningiomas are complex and involve losses on chromosomes like 1p (with loss of function of alkaline phosphatase (ALPL)), 6q, 10, 14q and 18q, as well as gains on multiple chromosomes. The relevant genes are still not completely known. Meningioma initiation is closely linked to the inactivation of one or more members of the highly conserved protein 4.1 superfamily, as current data indicate, which is including NF2 gene product Merlin / Schwannomin, protein 4.1B (DAL-1) and protein 4.1R. Anaplastic meningiomas show even more complex genetic alterations, including frequent alteration of the CDKN2A, p14ARF, and CDKN2B tumor suppressor genes at 9p21, as well as gene amplification on 17q23. A better understanding of the molecular mechanisms involved in meningioma pathogenesis may not only lead to the identification of novel diagnostic and**

prognostic marker but will also facilitate the development of new pathogenesis-based therapeutic strategies. Currently, the best-studied systemic treatment for patients with refractory meningioma is hydroxyurea. Blockade of the growth hormone receptor by Pegvisomant (with a known side effect profile) may soon hold a role. Long-term therapies holding promise include calcium channel blockers and gene therapies. A better understanding of the molecular mechanisms involved in meningioma pathogenesis may not only lead to the identification of novel diagnostic and prognostic marker but will also facilitate the development of new pathogenesis-based therapeutic strategies. Methods: In this detailed study, the most important features of meningioma, diagnosis, treatment, genetics, pathology and molecular pathogenesis are summarized and discussed along with an up-to-date overview about the molecular mechanisms involved in meningioma initiation and progression. Illustration of own data is provided with a detailed discussion of the clinical presentation of the patient and course, treatment plan and advices / recommendations after discharge. The most circumstantial predictors of refractory meningioma and novel systemic therapies in the treatment of the same tumors are presented in this study as well. The current literature was reviewed in this presentation and it was attempted to integrate and summarize available informations to determine a logical approach to these tumors. Results: Tumor location, atypical or malignant histologic subtypes, and staining for the Ki-67 protein (MIB-1 antibody) with a high labeling index are the best predictors of tumor recurrence. In addition, as metastases are unusual, but they do occur, review of the available evidence that has resulted in the current World Health Organization classification is topic of discussion as well. The treatment of choice is surgery, which is frequently successful in treating of these tumors, whereas there are usually two reasons that surgery might be ineffective: Firstly, tumor location or proximity to neurovascular structures may make a complete resection impossible. Secondly, the inherent biology of the tumor may give a particular meningioma a greater propensity for recurrence despite seemingly complete resection. Radiation therapy can be considered as an adjunctive treatment after surgical resection. In addition, the role of stereotactic radiosurgery is increasing, along with a possible role for brachytherapy. Novel systemic treatment options include angiogenesis inhibition, meningioma cell growth inhibition, blockade of growth factor effects, inhibition of intracellular secondary pathways, and gene therapies. Conclusions: Most meningiomas are slowly growing benign tumors that histologically correspond to World Health Organization (WHO I°). However, certain rare histological variants (clear cell, chordoid, papillary, and rhabdoid), as well as atypical (WHO II°) and anaplastic (WHO III°) meningioma show a more aggressive biological behavior and are clinically associated with a high risk of local recurrence and a less favorable prognosis. MIB-1 labeling index staining is a good predictor for refractory meningioma. Additionally, no histopathological unified classification scheme for atypical and anaplastic meningiomas was existent in the past, there are numerous inconsistencies in the literature. Treatment options for symptomatic meningiomas include primarily surgery, conventional external beam irradiation, stereotactic radiosurgery, and systemic therapies. Novel systemic treatment options include angiogenesis inhibition, meningioma cell growth inhibition, blockade of growth factor effects, inhibition of intracellular secondary pathways, and gene therapies. Currently, the best-studied systemic treatment, beside radiation therapy, for patients with refractory meningioma is hydroxyurea. Blockade of the growth hormone receptor by Pegvisomant is promising, whereas in vivo and in vitro studies have shown good results and it has a known and "acceptable" side effect profile, which can be managed easily. There are no effective chemotherapeutic agents available. A treatment algorithm is suggested for studies and investigations in the future.

Keywords: Cerebrospinal Fluid (CSF), Benign Grade I / Atypical Grade II / Anaplastic Meningioma (WHO grade III), certain rare histological variants (clear cell, chordoid, papillary, rhabdoid), Superior Sagittal Sinus (SSS), aggressive biological behavior, p53 expression, proto-oncogene, cytokeratin (CK), refractory meningiomas, staining for the Ki-67 protein (MIB-1 antibody), Vimentin, progesterone receptor (PR), estrogen receptor (ER), Merlin, Schwannomin, epithelial membrane antigen (EMA), Extracellular Matrix (ECM), gene amplification on 17q23, losses on 1p, 6q, 10, 14q&18q, gains on multiple chromosomes, alteration of CDKN2A, CDKN2B tumor suppressor genes at 9p21, radiation-/ and chemo-therapy, c-myc protein, hydroxyurea, messenger ribonucleic acid (mRNA), Pegvisomant, calcium channel blockers, gene therapy, growth hormone (GH), secretory meningioma (SM), Carcino-Embryonic Antigen (CEA), p14ARF, Odd`s ratio, Simpson classification, peritumoral brain edema (PTBE), VEGF, Matrix-Metalloproteinase (MMP), gross total resection (GTR), subtotal resection (STR), high-power microscopic fields (HPF), protein 4.1 tumor, loss of heterozygosity (LOH) on chromosome 22q, fluorescence in situ hybridization (FISH), epidermal growth factor receptor (EGFR), 3D-CT-Angiography (3D-CTA), Single Photon Emission Computed Tomography (SPECT), MR-Spectroscopy, MR-Angiography / Venography (MRA / MRV), Computed Tomography Venography (CTV), American Society of Anesthesiology (ASA), von Hippel-Lindau-Disease (VHL), Intraventricular Meningiomas (IVM), MIB 1-Labeliong Index (MIB 1 - LI), DAL-1– tumor suppression gene, psammomas / pseudopsammomas bodies, alkaline phosphatase (ALPL), Neuron-Specific Enolase (NSE), Claudin, E-Cadherin, Desmin, HNK-1 (Leu-7), Desmoplakin, Protein S-100, Desmin, HNK-1 (Leu-7), Claudin, Connexin.

1. INTRODUCTION

1.1 INCIDENCE, PREVALENCE, EPIDEMIOLOGY, ETIOLOGY AND RISK FACTORS:

Between 13 - 26% of all intracranial tumors are meningiomas [1-7, 9, 12, 24, 29, 48]. Meningiomas occur mostly in middle-aged or elderly patients, but they can also occur in younger patients with dysgenetic syndromes such as neurofibromatosis Type 2 (NF2). The annual incidence rate is approximately 6 per 100,000 [19] but some tumors are only discovered during autopsy. Often, they are diagnosed incidentally on brain imaging for unrelated complaints. A minority of these tumors demonstrate histopathological and clinical features suggesting an aggressive potential. These are the atypical and anaplastic meningiomas. The former constitute between 4.7 and 7.2% of meningiomas, whereas the latter account for 1.0 to 2.8% [9, 12, 24, 48]. Some series have shown that up to 2% of all benign meningiomas transform into malignant forms [2, 51], whereas up to 28.5% of all recurrent tumors will be found to be atypical or anaplastic [2, 18, 19]. Hug et al. [17] reported that the annual incidence of these tumors in the United States is approximately 150 to 225. There is a wide range in the prevalence data for these malignant forms because variable pathological criteria exist for their classification. Benign meningiomas are more prevalent in women, but atypical and anaplastic forms seem to be more common in men [29]. The atypical and anaplastic forms are also more common in the cerebral convexities [29]. Atypical meningiomas have been reported to occur after cranial irradiation for other tumors or conditions. These are usually found in younger patients. This complication was first reported in 1953, in a child receiving radiation therapy for an optic glioma. [9-17, 34-50, 102-114, 119-159].
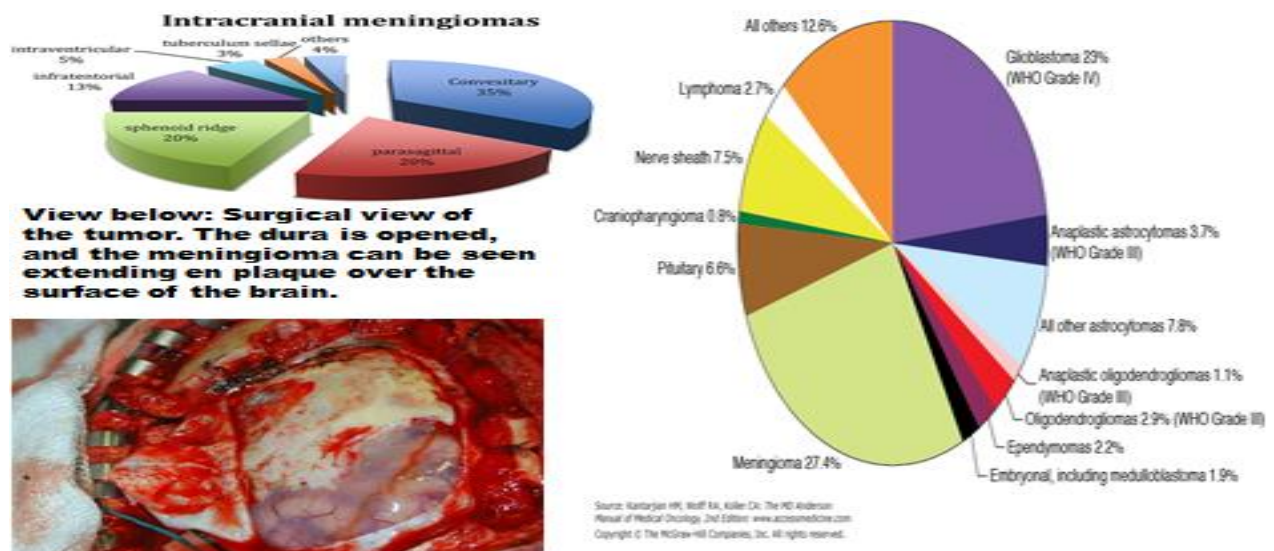
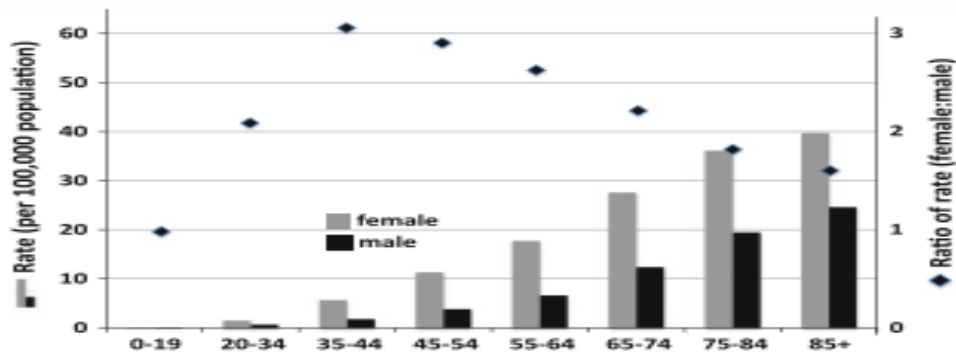**Information board 1: Meningiom aetiology, incidence and intraoperative view.**

Diagram 1: Age and gender-specific incidence rates (per 100,000 population) for meningioma in the United States (2002–2006) (Group TIS (2010) Brain tumour epidemiology: results of the international case–control study. Int J Epidemiol 39:675–694). The left Y-axis scale refers to the bar graphs. The ratio of female to male incidence is indicated by a diamond at each age group, and the axis for the ratio is along the right hand side of the figure. The peak ratio of 3.15, female:male, is among the 35–44 year age group.

1.2 RISK FACTORS:

Subsequently, children undergoing cranial radiation for medulloblastomas, astrocytomas, leukemia, and lymphoma have all been reported to develop meningiomas. These tumors have also been noted in patients who received low doses of irradiation for tinea capitis or after experimental radiation treatments during World War II. Dental x-rays have also been implicated. Often, multiple meningiomas are found in patients with these risk factors. Risk factors for meningiomas are mostly ionizing radiation, head trauma, hormones, viruses, inherited predisposition, abnormalities of chromosome 22 and Neurofibromatosis type II (NF2). [8, 11, 34, 45, 57-123, 134-156, 159-161].

1.2.1 Ionizing Radiation / X-Ray Exposition / Atomic Bomb Exposure:

At present, the primary environmental risk factor identified for meningioma is exposure to ionizing radiation (IR) with risks from six fold to tenfold reported [20–23]. At high dose levels, data exist for atomic bomb survivors in Japan was showing a greatly increased risk for meningioma [13-21]. Evidence also exists for lower dose levels. In one of the most well-known studies of IR and meningioma risk, children who were given radiation therapy (RT) for scalp ringworm in Israel between 1948 and 1960 (the Tinea Capitis Cohort), were observed to have a relative risk of almost 10 for meningioma [13-21, 25]. Other studies have linked the number of full-mouth dental radiographs to risk of meningioma (reviewed in [22-25]) although the sample sizes are limited and some subsequent studies (also small in size) did not replicate earlier studies. However, the most recent case/control study of 200 meningioma patients reported that patients reporting full-mouth X-rays had a significantly increased risk of meningioma although evidence for a dose response relation was lacking (P for trend = 0.33). RT for intra-cranial tumors has also been linked to meningioma risk. No recent large-scale studies of meningioma risk relative to ionizing radiation exist. Such studies are still highly relevant in the current era in which X-ray doses for dental and other procedures have decreased, since new radiographic procedures with significant exposure risks have been introduced, including computed tomography (CT). [1-9, 14-29, 55, 60-84, 90- 103, 114-119, 160-162)

1.2.2 Hormones:

An association between hormones and meningioma risk was suggested by many findings including the increased incidence of post-pubertal disease in women versus men (2:1) with the highest ratio of 3.15:1 during the peak reproductive years, the presence of estrogen, progesterone, and androgen receptors on some meningiomas, an association between breast cancer and tumor, indications that tumor change in size during the luteal phase of the menstrual cycle and pregnancy, and the regression of multiple meningiomas in a patient following cessation of estrogen agonist therapy [40-48, 51-60]. Despite these sentinel clues, meningioma is far from exhibiting a ''hormone-fed'' character in the clinic and epidemiologic measures of endogenous and exogenous hormones are not consistently associated with meningioma incidence. Researchers have only started to address the question of whether the use of exogenous hormones such as oral contraceptives (OC) and/or hormone replacement therapy (HRT) is associated with an increased risk of meningioma [15-19, 44-50]. Data from two cohort studies and several case/control studies exist. In a case/control study nested within the Nurse's Health Study (NHS) (including 125 cases of meningioma), the relative risk of meningioma associated with hormone use for pre-menopausal women was higher when compared with postmenopausal women who had never used hormones [10-19, 28-31, 33-49, 58-72, 88-100, 114-119, 123-139]. No excess risk was associated with past hormone use. No association was found for past or current use of oral contraceptives. The Million Women Cohort reported an increasing risk of meningioma with increasing body mass index, but no association with number of pregnancies or age at first birth [112-^8, 133, 136, 141-148, 159-162].

1.2.3 Head trauma:

Head trauma was suggested as a risk factor for meningioma since the time of Harvey Cushing, although the results across studies are not consistent. While some small case/control studies report an increased risk of meningioma associated with head trauma for both males and females, other studies report no such association. In a cohort study of 228 Danish patients hospitalized for concussion, skull fracture or other head injury between 1977 and 1992 and followed for an average of eight years, the standardized incidence ratio (SIR) for meningioma after the first year was 1.2, Odds-Ratio: 2.2. [49-66]
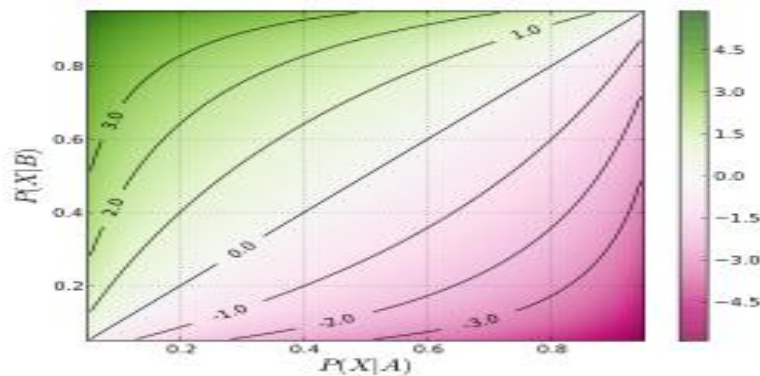
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Diagram 2: Odds-Ratio

1.2.4 Cell phone use:

The question of whether cell phone use is related to meningioma risk remains a question of great interest to the general public. At present, little evidence exists for an association between the two although sample sizes specific to meningiomas are relatively small, the follow-up time since commencement of cell-phone use is relatively short, and, in some instances, the measurement of cell-phone use is somewhat crude. If the latency times of 17–36 years observed in ionizing radiation studies on the epidemiology of meningioma [24, 55, 67-71] are taken as a guideline, the true extent of any possible relationship between cell phone use and meningioma risk may not be uncovered for decades and therefore this topic deserves continued attention. [1]

1.2.5 Association with breast cancer:

An association between breast cancer and meningioma has been examined in several studies. A number of explanations have been proposed for this association including the presence of common risk factors such as endogenous and exogenous hormones as well as shared genetic predisposition, including variants in DNA repair polymorphisms. A review of the literature as well as an analysis of the association between breast cancer and meningioma using the western Washington State cancer registry data was provided by Custer et al. The fact that studies which identify risk of breast cancer in women who had meningioma, and vice versa, both have similar magnitude increased risk suggests that there is not a causal relationship between these tumors, rather that they share the same risk factors such as gender, age, hormone induction, and possibly other demographic variables [1,120-129].

1.2.6 Occupation/diet/allergy:

Attempts to link specific chemicals with meningiomas in occupationally or industrially exposed groups have proved inconclusive. An international case/ control study found no association between diet and meningioma. Although a number of studies which examine the relationship between glial brain tumors and allergic disease such as asthma and eczema have found evidence for an association, little evidence has been found for such an association for meningioma. A meta-analysis however demonstrated a significant inverse relationship of meningioma with allergy when excluding the single study that was most heterogeneous from the others, and a large recent study showed consistent inverse risk with asthma, high fever, and eczema. [1]

1.2.7 Family history of meningioma:

The examined relationship between meningioma risk and family history of meningioma showed some studies. Malmer et al. (2003) examined cancer risk in spouses and first degree relatives of brain tumor patients in Sweden and reported that a meningioma diagnosis conferred a two fold increase in meningioma risk to first degree relatives (standardized incidence ratio [SIR] but not to spouses of affected individuals. An inverse association between risk and age at onset was observed with an SIR of 2.5 for probands less than 50 years of age versus 1.3 for probands older than 50 years of age. Similar analyses by Hemminki et al. (2009) using data from the Scandinavian Registry Databases, reveal an increased risk with increasing numbers of affected first degree relatives with persons having one or two first degree family members with meningioma and they were attributed to abnormalities of chromosome 22 and to inherited NF2 mutations. [1, 47-58, 105-131]
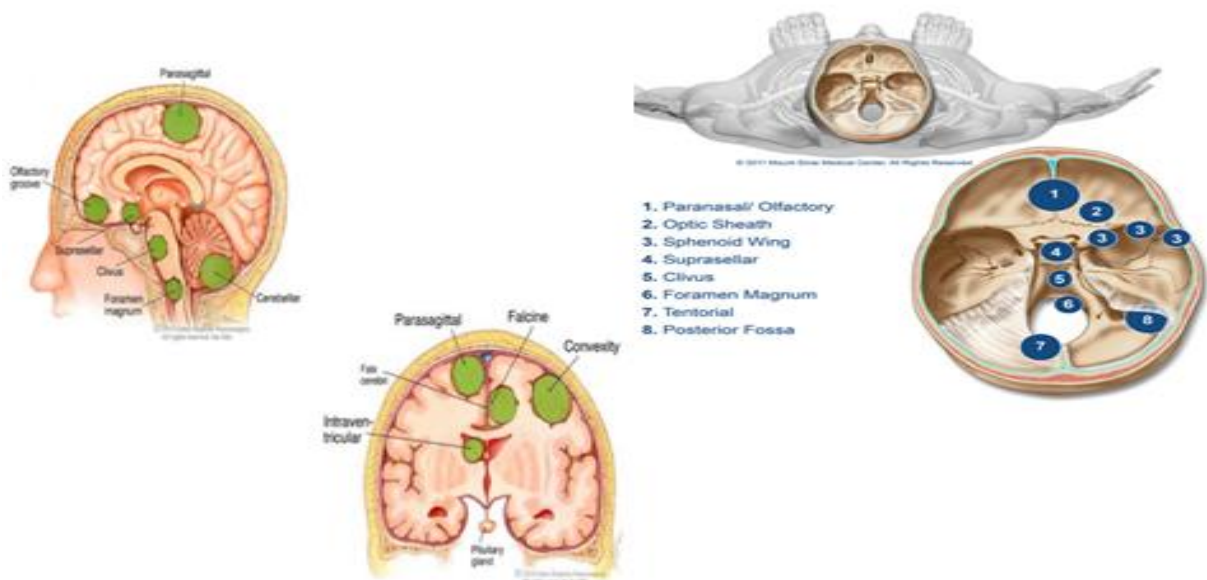
1.3 SPINAL MENINGIOMAS:

Meningiomas of the spinal axis have been identified from C1 to as distal as the sacrum. Their clinical presentation varies greatly based on their location. Meningiomas situated in the atlanto-axial region may present similarly to some meningiomas of the craniocervical junction, while some of the more distal spinal axis meningiomas are discovered as a result of chronic back pain. Surgical resection remains the mainstay of treatment, although advancements in radiosurgery have led to increased utilization as a primary or adjuvant therapy. Angiography also plays a critical role in surgical planning and may be utilized for preoperative embolization of hypervascular meningiomas.

Intradural extramedullary spinal cord tumors account for approximately two-thirds of all spinal cord tumors in adults. Meningiomas, neurofibromas, and schwannomas are the most common type of tumor in this type of location. Meningiomas represent about 40% of these tumors. The vast majority of spinal cord meningiomas are located in the thoracic region. This predominance of thoracic located meningiomas is seen only in females. Spinal meningiomas occur about 2.5 times more often in females than males; with approximately 75-85% arising in women. The female preponderance is thought to arise from sex hormones and / or other receptor types common to women. Some authors believe that progesterone and estrogen receptors actually have opposing prognostic indications in regards to meningiomas and that the expression of progesterone receptors alone in meningiomas, signifies a more favorable and biological outcome. They also found that either a lack of estrogen and progesterone receptors, or the presence of estrogen receptors in meningiomas, correlated with a more aggressive clinical behavior, progression, and recurrence. Hsu et al. reported the presence of progesterone receptors, even in a small subgroup of tumor cells, indicated a more favorable prognostic value for meningiomas. An interesting epidemiological feature of spinal meningiomas, is that not only are they more common in women, but there is a sharp rise in postmenopausal females. [6-13, 63]

1.4 LOCATION OF CRANIAL MENINGIOMAS:

90 % of meningioma are supratentorial . Most commonly location is: Fronto-parital, parasagittal convexities, falx, olfactory groove, tuberculum sellae and sphenoid wing. Majority of infratentorial tumors occurs at the cerebellopontine angle and foramen magnum / craniocervical junction. (Picture 1)

Picture 1: Localization of skull base meningioms (upper right images) and localization of cranial meningioms in general (lower left)

1.5 CLINICAL PRESENTATION OF MENINGIOMAS:

Most of meningiomas are asymptomatic. Symptoms are caused by compression of the adjacent brain. The symptoms can include gradual worsening headaches over weeks to months, blurred or double vision, loss of smell and taste, seizures, personality changes (perhaps noticed by others), speech difficulty, bowel or bladder dysfunction, brachio-facial deficits,

weakness in arms or legs, or even pins and needles and numbness in the limbs. Occasionally, an eye examination may reveal abnormalities, which lead to further investigation and diagnosis. Intermittently, meningiomas cause little or no symptoms and are discovered incidentally during a scan carried out for other reasons. [1-13]

1.6 ANATOMY AND FUNCTION OF MENINGOTHELIAL CELLS:

Like their neoplastic counterparts, normal meningothelial cells are morphologically and functionally diverse with some degree of overlap with both mesenchymal and epithelial cells (Information Board1). Based on comparative data from birds, it is suggested that the meninges are derived from neural crest in the telencephalon, cephalic mesoderm around the brainstem, and somitic mesoderm in the spinal cord. Arachnoid villi or Pacchionian granulations are polypoid invaginations forming the conduits for cerebrospinal fluid (CSF) drainage into the dural sinuses and veins. Histologically, the arachnoidal cap cells form the outer layer of the arachnoid mater and arachnoid villi (Figures 1 - 3), ranging from a single flattened fibroblast-like cell layer to epithelioid nests up to 10 cell layers thick. They are cytologically similar to meningioma tumor cells and are thus felt to represent their likely cell of origin. However, a more primitive progenitor cell has not been excluded as a possibility.

A thin basal lamina separates these cap cells from the underlying arachnoidal trabecular cells with thin, spider-like processes that form septations in the subarachnoid space.
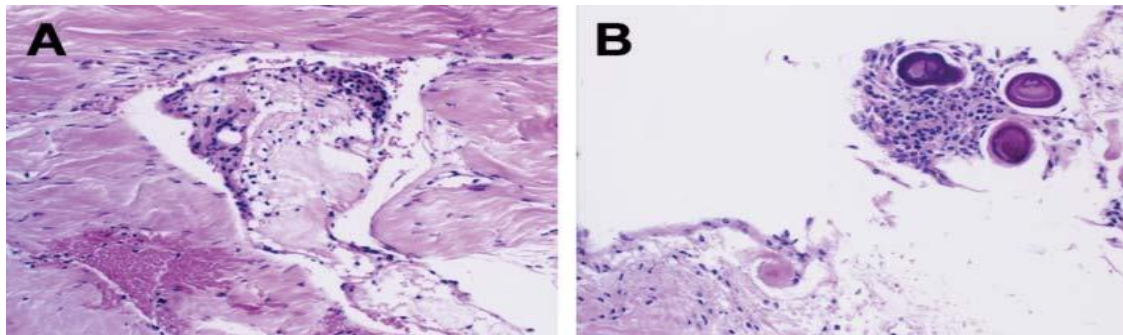

Figure 1: Arachnoidal cap cells forming epithelioid nests, whorls, and psammoma bodies in outer layer of arachnoid villi (A) and arachnoid mater (B).

Morphologically, ultrastructurally, and functionally, both non-neoplastic meningothelial cells and meningiomas are unique in their mesenchymal and epithelial-like attributes. [66-79, 88-96, 99, 101, 114-119].

The former includes spindled morphology and production of collagenous stroma, whereas the latter includes rounded or polygonal cytology, numerous intercellular junctions, expression of epithelial membrane antigen (EMA), and secretory functions (Information Board 1-3). [13-19, 22-29, 32-33, 35-39, 46-59]

1. Anatomic barrier with cellular wrapping/ensheathing
   - Arachnoid cap cells line outer layers of arachnoid mater and villi
   - Arachnoid trabecular cells line subarachnoid space
   - Part of CNS-CSF and blood-CSF barriers
   - Part of choroid plexus stroma (tela choroidea)
   - Ensheath proximal portion of nerve roots
   - Tendency for cells to wrap around each other, vessels, and other cell types
2. Conduit for CSF drainage/absorption into dural sinuses/veins (arachnoid villi)
   - Help regulate intracranial pressure
   - Participate in CSF homeostasis
3. Fibroblast/mesenchymal-like functions
   - Production of collagen and other stromal proteins
4. Epithelial-like/secretory functions
   - Intercellular communication via desmosomes and other junctions
   - Synthesis/Secretion of major CSF proteins (e.g., prostaglandin D-synthase, IGF-II, IGFBP-II, apo-E, β2-microglobulin, etc.)
   - Secrete glioneuronal differentiation and proliferation factors
   - May secrete hyperostotic factors (e.g., alkaline phosphatase)
   - Secrete chemoattractants involved in EGL migration/cerebellar development
5. Monocyte-like functions
   - Form multinucleated giant cells
   - Emperipolesis (i.e., lymphoplasmacytic engulfment)
   - HLA-DR expression
   - Participation in foreign-body reactions and meningeal rheumatoid nodules
6. Trophic support and byproduct detoxification for glial and neuronal cells
7. Participate in reactive/reparative processes (e.g., meningeal hyperplasia)

Information Board 2: Proposed functions of meningothelial cells

Prominent mesenchymal features are seen in the fibroblastic and metaplastic meningiomas at the benign end and sarcomatoid morphology at the malignant end of the spectrum. The most advanced epithelial phenotype is found in the secretory variant of meningioma representing frank glandular metaplasia with microvilli, cilia, intraluminal secretions and immunoreactivity for cytokeratin and carcinoembryonic antigen (CEA). Similarly, some anaplastic meningiomas with epithelioid features resemble metastatic carcinomas. Lastly, meningothelial cells may display some monocytelike properties and may participate in a variety of reactive and inflammatory processes. [140-148, 150-161].

Grade	Designation	Meningioma
I	Typical	Meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, clear cell, choroid, lymphoplasmacyte-rich, metaplastic
II	Atypical	Papillary
III	Anaplastic	Malignant

* Based on WHO classification 1993. Sekhar LN, Levine ZT, Sarma S. Grading of meningiomas. *J Clin Neurosci.* 2001;8(suppl 1):1-7.

Information Board 3: Pathologic Classification of Meningiomas*

1.7 MENINGOTHELIAL HYPERPLASIA:

The process of meningothelial hyperplasia is currently poorly defined and it is not known whether this represents a precursor stage in the tumorigenesis of meningiomas. Nevertheless, it is inferred for meningothelial proliferations >10 cell layers thick, associated with a discernible inciting event, such as trauma, hemorrhage, chemical irritation, inflammation, or neoplasia (Fig. 1 - 4). Other meningeal-based reactive processes include granulation tissue/scar formation, inflammation, and vascular proliferation. For example, the enhancing dural tail at the edge of meningiomas often consists of nothing more than hypervascular dura. In others, small meningothelial nests may also be found and it may be difficult to ascertain whether they are normal, hyperplastic, or neoplastic in nature. [44-52, 58-67, 69-80, 83-91, 100, 111-119].

1.8 MENINGIOMA PATHOLOGY / BIOLOGICAL SPECTRUM OF MENINGIOMAS:

Meningiomas (WHO I) are considered as benign tumor. Whereas many are slow-growing and surgically curable tumors corresponding histologically to World Health Organization (WHO I), an important subset is associated with increased morbidity and mortality.

These atypical (WHO grade II) and anaplastic (WHO grade III) examples are clearly more aggressive, though even some of the histologically benign meningiomas recur unexpectedly, disfigure the patient, invade or compress critical anatomic structures, and significantly impair neurologic function. Several prognostic variables are now recognized, the two most important being histologic grade and extent of surgical resection. For example, overall 5-year recurrence rates are estimated at 12% for gross total (GTR) vs. 39% for subtotal resection (STR).

Combined with histologic grading, the predictive accuracy improves further, such that the 5 year rates are 5% for GTR benign (WHO grade I) vs. 40% for GTR atypical (WHO grade II) meningiomas. Even some of the histologically benign meningiomas recur after seemingly complete resection though, with long-term follow up studies suggesting recurrence rates as high as 19% at 20 years. [19, 23, 44-51, 70, 99-118]
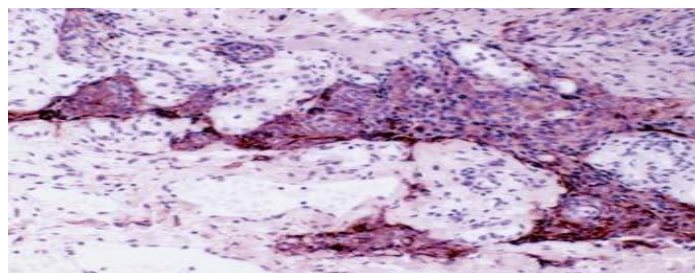

Figure 2: Focus of epithelial membrane antigen-positive meningothelial hyperplasia in region of tela choroidea. There was trauma to the choroid plexus due to its entrapment within an intraventricular shunt.

1.9 HISTOPATHOLOGY:

The microscopic appearance of meningiomas is remarkably diverse, as evidenced by the 13 variants and three grade categories recognized in the current WHO classification. The prognostic value of the Ki-67/MIB-1 labeling index (LI) in human meningiomas was reported in previous studies and it was showed, there awas positive correlations between Ki-67/MIB-1 LI and histological malignancy grade. The average mean labeling indices were 3%, 8%, and 17% for grade I–III meningiomas, respectively. Concerning recurrence, meningiomas with a labeling index beyond 4% may indicate an increased relapse rate. Consequently, Ki-67/MIB-1 LI represents a useful predictor of tumor grade and risk of a recurrence, however, it must be interpreted cautiously in the individual tumor.

The three most common variants are meningothelial, transitional, and fibroblastic, with combinations of two or more patterns frequently encountered. Uncommon subtype of benign meningiomas is secretory meningioma (SM), which is containing eosinophilic and periodic acid-schiff (PAS)-positive globular intracellular pseudopsammomas. Four meningioma subtypes are considered innately more aggressive and have been assigned either to WHO grade II (clear cell meningioma, chordoid meningioma) or WHO grade III (papillary meningioma, rhabdoid meningioma). These variants are rare, each accounting for less than 1% of all meningiomas. Therefore, relatively little clinical, pathologic and molecular data is available on these subtypes compared with classic variants. Meningothelial meningiomas are characterized by rounded or polygonal epithelioid cells arranged in lobules or whorls. Intercellular junctions often appear fuzzy or ill-defined imparting a syncytial-like pattern (Figure 3A). Ultrastructurally, this pattern is explained by the presence of numerous cytoplasmic processes interdigitating between cells like interlocking pieces of a jigsaw puzzle. Other common cytologic features include clear intranuclear vacuoles, intranuclear pseudoinclusions (i.e., invaginations of cytoplasm into the nucleus), and moderate quantities of eosinophilic cytoplasm. Fibrous or fibroblastic meningiomas are characterized by spindled cells arranged in fascicles or storiform architecture with interspersed collagen deposition (Figure 3B). Transitional meningiomas are characterized by mixed or intermediate features of meningothelial and fibroblastic meningiomas. Whorls and psammoma bodies are particularly common in this subtype and it is perhaps the most classic of all meningioma patterns (Figure 3C). [65, 69, 72, 77, 89, 115-125, 141-149, 155-160]
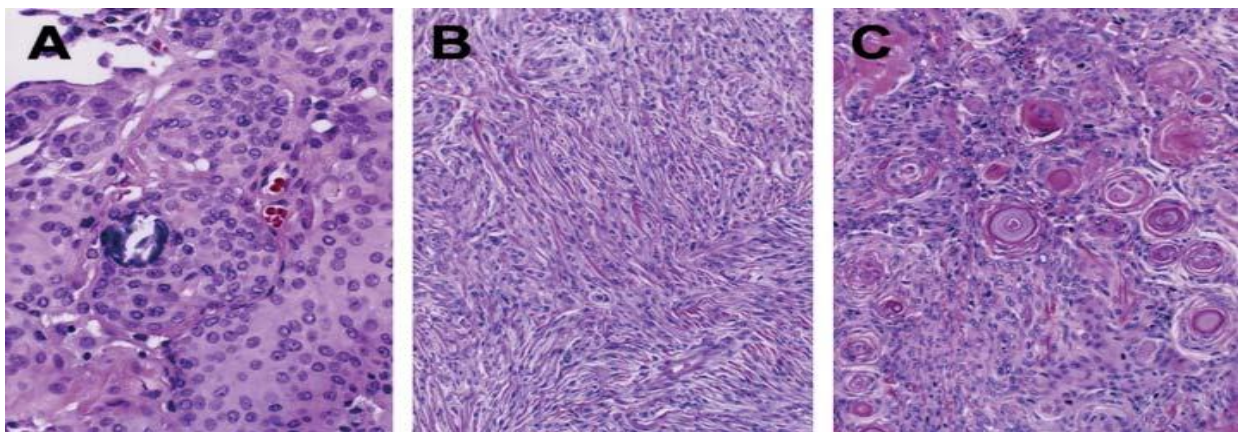

Figure 3: Common histologic variants of benign meningiomas (WHO grade I). (A) Meningiothelial variant with lobules of epithelioid cells and ill-defined borders imparting a syncitial-like pattern. (B) Fibrous/fibroblastic variant with intersecting fascicles of spindled cells and collagen deposition. (C) Transitional variant with combined or intermediate features, epithelioid and spindled cells, abundant whorls, and psammoma bodies.

1.10 MENINGOSARCOMA WHO GRAD IV:

This is a rare form of diffuse malignant mesenchymal tumor with disseminating growth pattern, which does not show histopathologically features of meningothelial tumor cells (Jeffry Tobias et al, 2012). An autopsy case of meningiosarcoma was reported by Haruo Ohkubo in November 2008: A10-year-old girl with a primary leptomeningeal tumor was presented with a 5-week history of increased intracranial pressure, progressive cranial nerve deficits, and spinal compression signs. At autopsy, the brain and spinal cord showed diffuse neoplastic involvement of the leptomeninges. The tumor was composed of small cells with a high nucleus / cytoplasm ratio, which were immunoreactive for vimentin but not for epithelial membrane antigen or cytokeratin. [12-17, 24-35, 41-49]
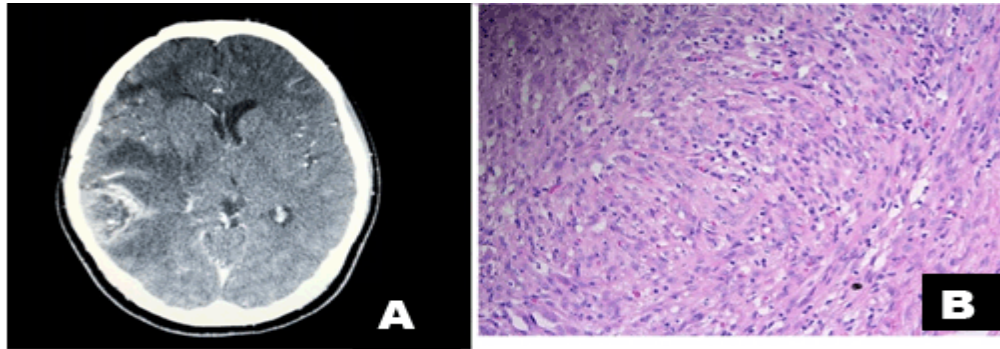
Picture 1: Case of "Meningiosarcoma".

1.11 MENINGIOMATOSIS:

This is the presence of multiple meningioma tumors, whereas the tumors are not easily countable, especially in the MRI. (56-70, 88-111)

1.12 MENINGIOMA EN PLAQUE:

Keya-Basu et al (2010) reported this tumor a morphological subgroup within the meningiomas defined by a carpet- or sheet-like lesion that infiltrates the dura and sometimes invades the bone. Differential diagnosis includes fibrous dysplasia, osteoma, and osteoblastic metastasis.
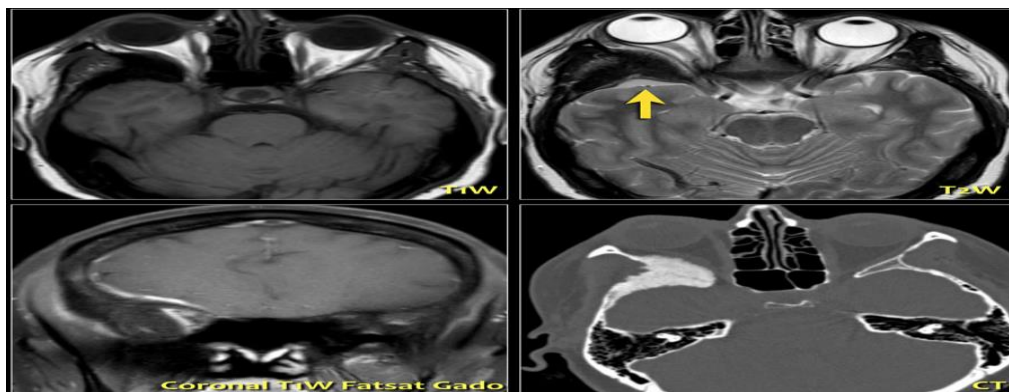
Picture 2: Meningioma en plaque

1.13 MENINGEOSIS CARCINOMATOSA UND NEOPLASTICA:

Masuhr, Karl F. et al. (2013), that 3 -5% of all patients with malignancies can develop leptomeningeal carcinomatosis, meningiosis carcinomatosa / neoplastica and meningitis neoplastica during the course of their disease. Signs and symptoms are usually pleomorphic. Magnetic resonance imaging (MRI) of the central nervous system and lumbar puncture are the cornerstones of diagnosis. Therapeutic decisions should take overall prognosis into account.

2. CASE ILLUSTRATION

2.1 HISTORY AND CLINICAL PRESENTATION:

A 54-year-old man began to have "shoulder problems" and was seen by a physical therapist, who believed that the symptoms were more consistent with a stroke since they included right hemiparesis and cognitive changes. (Case presented and treated in Klinikum Osnabrück, Germany, 2010-2013).
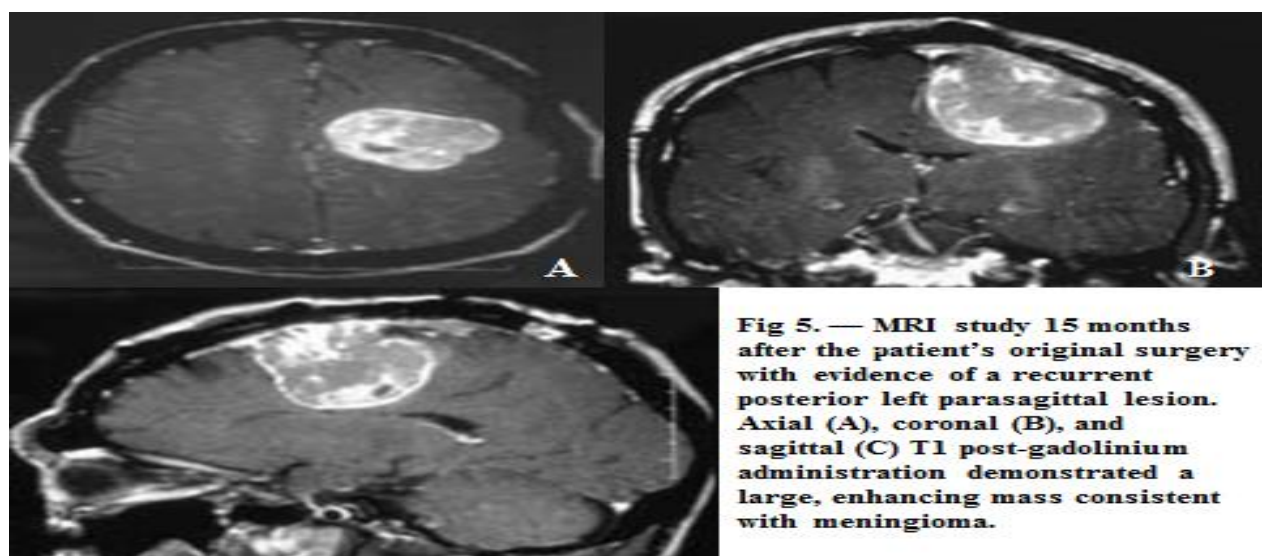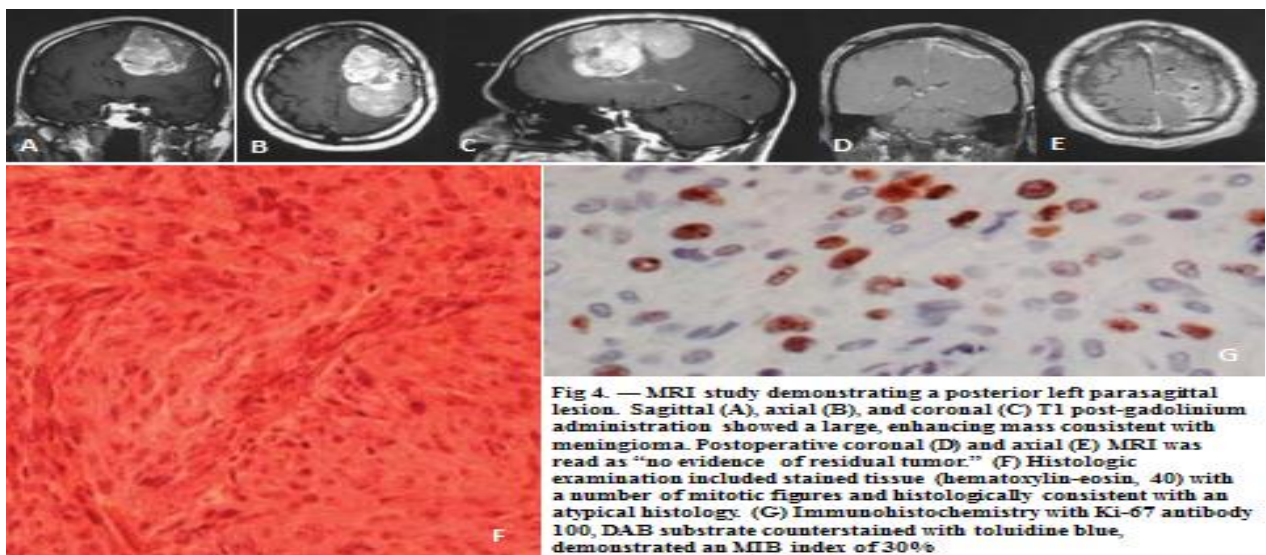
2.2 TREATMENT AND CLINICAL COURSE:

The patient was returned to his internist, and magnetic resonance imaging (MRI) demonstrated a posterior left parasagittal meningioma (Fig 4A-C). He was then admitted to the hospital and underwent a cerebral angiogram with subsequent embolization. The following day, a frameless stereotactic-guided craniotomy and resection were performed.

The postoperative MRI was reported as "no evidence of residual tumor" (Fig 4D-E) but the tumor pathology showed a number of mitotic figures and an MIB index of 30%, with a diagnosis of atypical meningioma (Fig 4F-G). The patient made a full recovery and returned to his prior occupation of construction work. His follow up imaging studies at 6 months were without residual tumor. However, 15 months after his original surgery, he experienced a recurrence of his original symptoms. An MRI was performed and revealed large recurrence of tumor (Fig 5A-C). Repeat angiogram, embolization, and surgery were performed, with sacrifice of the superior sagittal sinus.

Histopathologically, the tumor was unchanged, with at least 5 mitotic figures per high power field and an MIB index of 50%. His symptoms again resolved and radiation therapy was performed to 54 Gy. He returned to work and was mostly asymptomatic. Surveillance imaging revealed some extracranial nodularity (Fig 6A-B), and these were followed with serial imaging.

However, 24 months after his initial surgery, they had grown considerably (Fig 6C). A third resection performed in conjunction with plastic surgery. This required duraplasty, cranioplasty, resection of the invaded scalp, and a latissimus dorsi muscle flap. The pathology was unchanged but showed extensive invasion of the overlying scalp, bone, and dura (Fig 6D-F). Initially, postoperative films demonstrated no evidence of tumor recurrence (Fig 6G-H), but at 9 months from the last surgery, the films showed small enhancing skin nodules consistent with tumor recurrence. The patient required intensive rehabilitation after this last surgery and was back to his initial functional status and he was counselled on possibly needing stereotactic radiosurgery, chemotherapy with RU486 or hydroxyurea, and / or repeat surgery.

Fig 4. — MRI study demonstrating a posterior left parasagittal lesion. Sagittal (A), axial (B), and coronal (C) T1 post-gadolinium administration showed a large, enhancing mass consistent with meningioma. Postoperative coronal (D) and axial (E) MRI was read as "no evidence of residual tumor." (F) Histologic examination included stained tissue (hematoxylin-eosin, 40) with a number of mitotic figures and histologically consistent with an atypical histology. (G) Immunohistochemistry with Ki-67 antibody 100, DAB substrate counterstained with toluidine blue, demonstrated an MIB index of 30%

Fig 5. — MRI study 15 months after the patient's original surgery with evidence of a recurrent posterior left parasagittal lesion. Axial (A), coronal (B), and sagittal (C) T1 post-gadolinium administration demonstrated a large, enhancing mass consistent with meningioma.
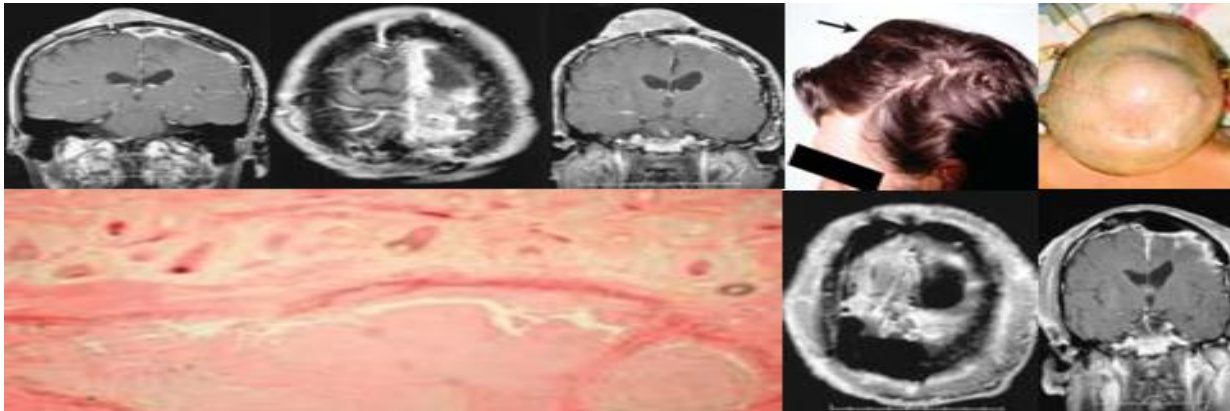
Fig 6. — MRI study 5 months after the patient's second surgery, 20 months after the original surgery with evidence of a extracranial nodularity and possible recurrence of his tumor. Coronal (A) and axial (B) T1 post-gadolinium administration demonstrated a small amount of enhancement consistent with possible recurrent meningioma. Three months later this had progressed, demonstrating tumor recurrence. (C) Coronal T1 post-gadolinium-enhanced lesion appeared largely extracranial. (D) Lateral photograph of the patient's head showed a bump at the sight of prior surgery. (E) Intraoperative photograph of the patient's head after shaving showed a visible tumor mass subcutaneously below the prior skin incision. (F) Hematoxylin-eosin stained tissue (× 40) demonstrated extensive invasion of the overlying scalp, bone, and dura. Immediate postoperative axial MRI (G) and coronal MRI (H) once again were believed to show no residual tumor.

2.3 EVALUATION OF THE PRESENTED CASE:

Complete surgical resection is the first-line therapy for meningiomas. However, tumor location and biological aggressiveness can make a "surgical cure" impossible. Treatment options for these so-called refractory meningiomas include further surgery, conventional external beam irradiation, stereotactic radiosurgery, and systemic therapies. Tumor location, atypical or malignant histologic subtypes, and staining for the Ki-67 protein (MIB-1 antibody) with a high labeling index (like in this presented case), are the best predictors of tumor recurrence. Novel systemic treatment options include angiogenesis inhibition, meningioma cell growth inhibition, blockade of growth factor effects, inhibition of intracellular secondary pathways, and gene therapies. Currently, hydroxyurea is the best-studied systemic treatment for patients with refractory meningiomas. Blockade of the growth hormone receptor by Pegvisomant may soon hold a role because *in vivo* and *in vitro* studies have shown good results and Pegvisomant has a known side effect profile. Long-term therapies holding promise include calcium channel blockers and gene therapies.

3. PATHOLOGICAL CLASSIFICATION AND MOLECULAR PATHOGENESIS:

3.1 ELEMENTARY FEATURES:

Meningioma grading was reported previously and was controversial. In the 1977 edition of the classic Russell and Rubinstein textbook, Pathology of Tumors of the Nervous System, no designation for atypical meningioma was included. However, the authors did state that meningiomas that invaded the brain and/or metastasized were likely to be malignant. In 1979, the WHO grouped meningiomas as either benign or anaplastic/malignant. The latter included all meningiomas that displayed "anaplastic features" but that had not developed into a sarcoma.

Perry et al. reported 2 studies from Mayo Clinic. were reported regarding grading of meningiomas. In the first study, meningiomas from 581 consecutively treated patients were analyzed and grading recommendations were provided based primarily on those cases in which a gross total resection (n = 463) was accomplished. The histological features assessed included cellular pleomorphism, nuclear atypia, presence of macronuclei, small cell cytology, sheeting (pattern less architecture), atypical mitoses, necrosis, maximal mitotic rate, level of cellularity, and brain invasion. All patients considered, brain invasion, sheeting, absence of nuclear atypia or cellular pleomorphism, and a maximal mitotic rate of >4 mitoses/10 high-power microscopic fields (HPF) ($>2.5/mm^2$) were univariately associated with decreased recurrence-free survival. These factors, as well as necrosis and macronuclei, were statistically significant in the gross total resection subset, whereas hypercellularity (>53 nuclei/HPF; $>118/mm^2$) alone proved significant in the subtotally resected cohort.

Fig. 1 above illustrates brain invasion by a benign meningioma. When brain invasion was removed from consideration, an independent and especially strong association of reduced recurrence-free survival with a maximal mitotic rate of $> 4/10$ HPF ($>2.5/ mm^2$) was noted. The absence of cellular pleomorphism, a far more subjective criterion, also remained

independently significant, as did various histological features when found in combination. Of greatest statistical power, and prognostically significantly independent of mitotic rate, was the presence of at least 3 of the following 4 variables: sheeting, macronuclei, small cell formation, and hypercellularity. The authors recommended that "atypical" meningiomas be defined as those exhibiting the latter profile or a minimum of four mitoses per HPF. (See Fig. 7 - 12). In their second study, Perry et al. [11-29] focused on the significance of brain invasion and other traditional indices of malignancy in meningiomas by assessing 116 cases that had been branded "malignant" on the basis of histologically confirmed brain infiltration, extracranial metastases, or frank morphological anaplasia (defined as having >20 mitotic figures/10 HPF or exhibiting a loss of meningothelial differentiation resulting in carcinoma-, sarcoma-, or melanoma-like histology). Fig. 3 above demonstrates these features in an anaplastic meningioma. In fact, only 17% of brain-invasive meningiomas exhibited frank anaplasia; 23% were otherwise benign in appearance, whereas the majority (61%) qualified as atypical by the criteria enumerated in the authors' previous analysis. Although brain invasion proved to be a powerful predictor of reduced recurrence-free survival, the worst prognosis was attached to meningiomas evidencing frank histological anaplasia as previously defined, whether invasive or not. By contrast, survival differences for "brain-invasive, otherwise benign" and "brain-invasive, otherwise atypical" meningiomas were not statistically significant, nor did these invasive but histologically non-anaplastic lesions as a group differ significantly from otherwise atypical meningiomas without brain invasion, in terms of overall or recurrence-free survival. The increased risk of extracranial metastases attached to histologically anaplastic meningiomas was a rare event in the experience of these authors. (Tables 1 & 2).

TABLE 1. Meningioma grading: The Mayo Clinic scheme[a]
Pathological criteria for the diagnosis of atypical meningiomas
≥ 4 mitoses/10 HPF (≥ 2.5/mm²)
    Or at least three of the following features:
Sheeting
Macronuclei
Small cell formation
Hypercellularity (≥53 nuclei/HPF; ≥118/mm²)
Brain invasion
Pathological criteria for the diagnosis of anaplastic meningiomas
≥20 mitotic figures/10 HPF (≥ 12.5 mm²)
    Or
Focal or diffuse loss of meningothelial differentiation resulting in carcinoma-, sarcoma-, or melanoma-like appearance

[a] HPF, high power microscopic fields (43,44).

Additionally, in one instance, a benign meningioma was found to be metastatic. This is a recognized, though most exceptional, phenomenon (benign metastasizing meningiomas) (Fig. 7 and 8).
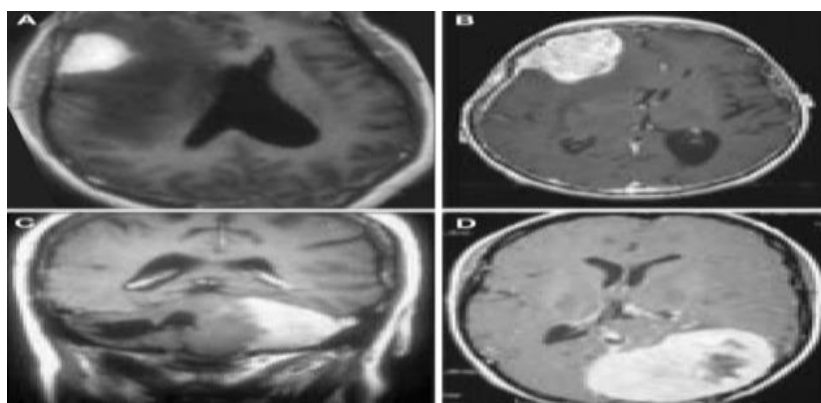

FIGURE 7: T1-weighted images of the brain with contrast showing a variety of atypical meningiomas with associated radiographic features. A, Severe peritumoral edema with mass effect and midline shift. B, mushrooming. C, wisps of contrast enhancement within the brain parenchyma consistent with brain invasion. D, necrosis.

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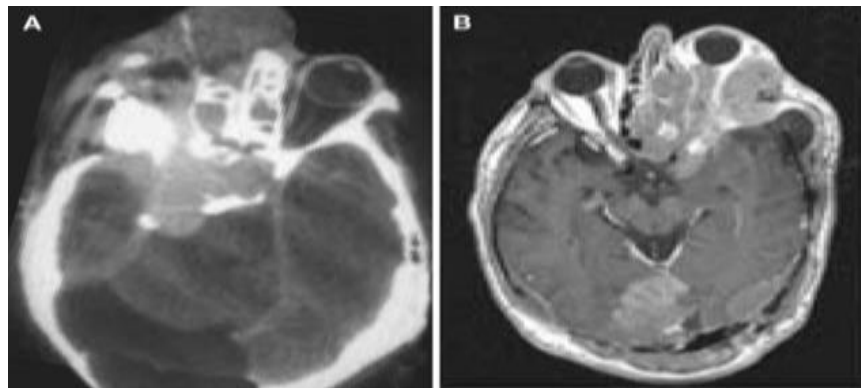
FIGURE 8: A, axial computed tomographic scan of the brain with contrast showing an anaplastic meningioma causing extensive bony erosion and invasion. B, axial T1-weighted image with contrast showing a large anaplastic meningioma infiltrating the orbit and sinuses, causing severe exophthalmos.

In 2000, WHO revised the meningioma subtypes grading. The Mayo Clinic criteria for the designations of atypical and anaplastic meningioma were endorsed with little modification. The WHO did not specifically recommend terming atypical those otherwise benign lesions that invade brain but acknowledges that brain infiltration increases the risk of recurrence. Additionally, necrosis was enumerated as a criterion of atypical meningioma when found in combination with other features.

Meningiomas with low risk of recurrence and aggressive growth (WHO grade I)
Meningothelial meningioma
Fibrous (fibroblastic) meningioma
Transitional (mixed) meningioma
Psammomatous meningioma
Angiomatous meningioma
Microcystic meningioma
Secretory meningioma
Lymphoplasmacyte-rich meningioma
Metaplastic meningioma

Meningiomas with greater likelihood of recurrence and/or aggressive behaviour (WHO grade II)
Atypical meningioma
Clear-cell meningioma
Chordoid meningioma

Meningiomas with greater likelihood of recurrence and/or aggressive behaviour (WHO grade III)
Anaplastic (malignant) meningioma
Rhabdoid meningioma
Papillary meningioma
Meningiomas of any type or grade with high proliferation index and/or brain invasion

Table 2: The different histological meningioma variants grouped by WHO grade

Specifically, it is suggested that meningiomas not showing increased mitotic activity be termed atypical when exhibiting at least three of the following five features: increased cellularity, prominent nucleoli, small cell cytology, sheet-like or patternless growth, and spontaneous or geographic necrosis (i.e., zonal, as opposed to single cell, necrosis in the absence of prior embolization). The WHO classification specifically recognizes the increased biological potential of clear cell, chordoid, rhabdoid, and papillary meningiomas while acknowledging that elevated proliferative indices, as defined most commonly by immunohistochemical detection of the Ki-67 antigen, may constitute evidence of aggressive capacity in meningiomas of any histological subtype or grade. In meningiomas, a fairly good correlation exists between histological grading and Ki-67 antigen expression as determined by immunoreactivity with the MIB-1 monoclonal antibody. This warrants caution in interpreting an individual MIB-1 index. These conclusions stem from studies that used classification systems differing from WHO 2000 or Perry et al. to grade their lesions. Therefore, Perry et al. used their criteria to initially grade meningiomas pathologically, and then determined the MIB-1 labeling indices. They found that the MIB-1 labeling index was only valuable when evaluating tumors with borderline atypia. In such a case, an index of >4.2% would classify the tumor as atypical. Fig. 10 - 12 show MIB-1 labeling in an atypical meningioma. [14, 19, 34,-58, 67-90, 106-130, 155-161]. The Simpson's criteria for grading depend on the related extent of tumor resection and the associated recurrence rates.

| Grade	Tumor Resection	Recurrence Rate
I	Macroscopically complete removal of dura, bone	9%
II	Macroscopically complete removal, dural coagulation	19%
III	Complete tumor resection, dura not coagulated	29%
IV	Partial removal	44%
V	Simple decompression	

* Based on Simpson grade.[3]

Information Board 4: Resection-Based Classification of Meningiomas (Simpson Grading)

Nagashima et al (2002) investigated the expression of c-myc protein and messenger ribonucleic acid (mRNA). In their series of 20 meningiomas, 10 benign tumors did not express this protein or mRNA, whereas all 10 atypical and anaplastic tumors did. Furthermore, they showed that the frequency of c-myc immunopositive cells positively correlated with Ki-67 proliferative indices. [45, 69, 73-79, 88-100, 111-133].

3.2 PATHOLOGICAL CHANGES AT PROGRESSION:

Typical feature of meningiomas are psammoma bodies (KEPES, J. (Apr 1961). "Observations on the formation of psammoma bodies and pseudopsammoma bodies in meningiomas.". J Neuropathol Exp Neurol 20: 255-62). (Picture 3). In their initial study of grading criteria for meningiomas, Perry et al. [34-49, 114-145] additionally reviewed pathology at recurrence. Slides from 35 patients were available for review: 29 remained at the same grade, two became atypical from benign, and four were classified as benign, but were initially atypical. Another review of 936 patients by Jaaskelainen et al. revealed that 70 meningiomas that were initially benign recurred: 60 stayed benign, but 10 showed atypical or anaplastic changes. Additionally, initially atypical lesions recurred; four were found to be anaplastic and one sarcomatous. Thus, all of these tumors can progress biologically.
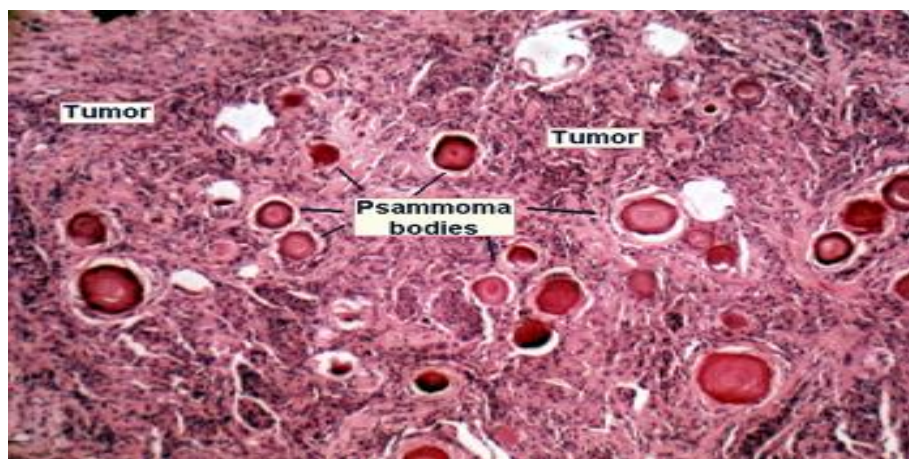
Picture 3: Psammoma bodies in meningioma

3.3 BENIGN MENINGIOMA, WHO GRADE I:

80-90 % of excised tumors are histologically benign, unassociated with excess mortality when gross totally resected, do not fulfill criteria for atypical/anaplastic grades & composed predominantly of any histologic pattern, other than clear cell, chordoid, papillary, or rhabdoid. (See Fig. 9) Dural, bone, soft tissue, paranasal sinus, and even vascular/dural sinus invasion are not uncommon and do not warrant a higher histologic grade. But brain invasion is considerably rarer and has grading implications. [29-49, 69]
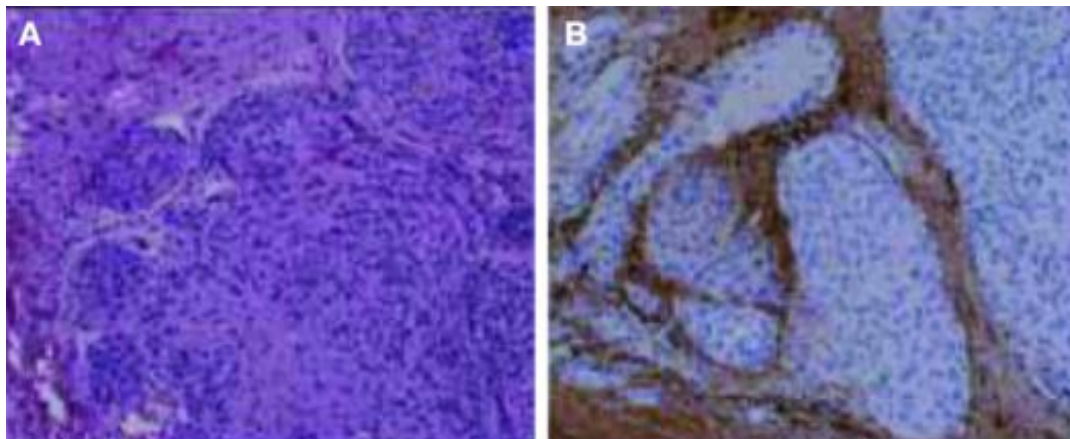
Figure 9: Histopathological images of a benign meningioma illustrating invasion of the brain parenchyma. A, Hematoxylin and eosin stain. B, Glial fibrillary acidic protein stain.

3.4 ATYPICAL MENINGIOMA, WHO GRADE II:

Atypical meningiomas account for roughly 15–20% of cases and are associated with a markedly increased risk of recurrence and a small, but statistically significant increased risk of death, when compared with control age and sex-matched U.S. cohorts. Statistically, the strongest single criterion associated with recurrence is an elevated proliferation index, defined as > 4 mitoses per 10 consecutive high-powered fields (HPF), regardless of whether this finding is focal or widespread. It is important to note that despite the name 'atypical meningioma', nuclear atypia is not particularly reliable [33-59, 66-90], given that degenerative atypia may be encountered in otherwise benign meningiomas, similar to that seen in ancient schwannomas. In the absence of increased mitotic activity, atypical meningiomas are diagnosed by the presence of either brain invasion or at least 3 of 5 other criteria (See Tables 3&4).

Table 3 A: WHO grading criteria for meningiomas (Louis 2000)

Benign meningioma (grade I)
- Histologic variant other than clear cell, chordoid, papillary, and rhabdoid
- Lacks criteria of atypical and anaplastic meningioma

Atypical meningioma (grade II) (any of 3 criteria)
- Mitotic index ≥4/10 high powered fields (HPF)
- At least 3 of 5 parameters:
  Sheeting architecture (loss of whorling and/or fascicles)
  Small cell formation (high N/C ratio)
  Macronucleoli
  Hypercellularity
  Spontaneous necrosis (i.e., not induced by embolization or radiation)
- Brain invasion

Anaplastic (malignant) meningioma (grade III) (either of 2 criteria)
- Mitotic index ≥20/10 HPF
- Frank anaplasia (sarcoma, carcinoma, or melanoma-like histology)

Meningioma subtypes

	WHO grade
Meningiomas with low risk of recurrence or aggressive growth:	
Meningothelial	I
Fibrous (fibroblastic)	I
Transitional (mixed)	I
Psammomatous	I
Angiomatous	I
Microcystic	I
Secretory	I
Lymphoplasmacyte-rich	I
Metaplastic	I
Meningiomas with greater likelihood of recurrence and/or aggressive behavior:	
Atypical*	II
Clear cell (intracranial)	II
Chordoid	II
Rhabdoid	III
Papillary	III
Anaplastic (malignant)	III
Meningiomas of any subtype with high proliferative index	

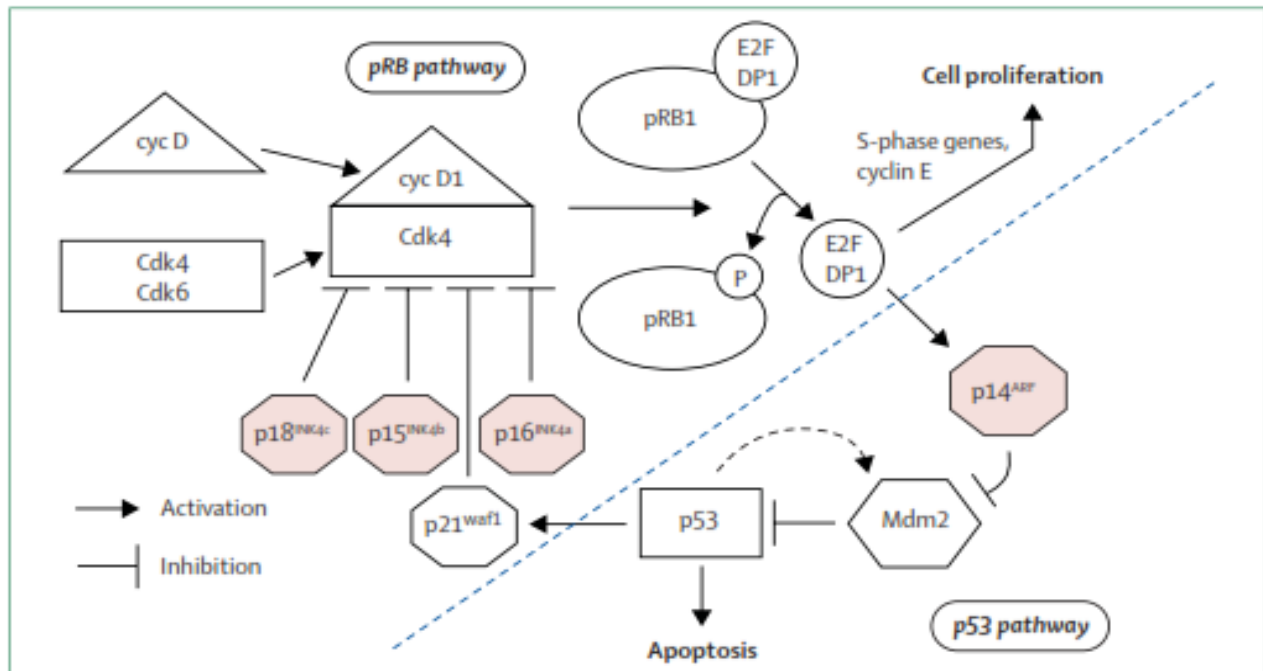**Table 3 B: WHO classification for Meningiomas**

Table 4: Interrelationships of pRB and p53 cell cycle regulation pathways: Anaplastic meningiomas exhibit frequent CDKN2A (encoding p16 ^{INK4a}), ARF, and CDKN2B (encoding p15) homozygous deletions and mutations, indicating that inactivation of the G1/S-phase cell-cycle checkpoint is essential for malignancy. CDKN2C (encoding p18) is only rarely mutated in cases of atypical or anaplastic meningioma. While INK4a, INK4b, and INK4c inhibit cell-cycle progression at the G1/S-phase checkpoint through negative eff ects on the cyclin-dependent kinases Cdk4 and Cdk6, ARF functions as a negative regulator of the Mdm2 oncoprotein, thereby inhibiting p53 degradation. Involved molecules in meningioma progression are shaded in grey. More informations below.

In contrast to the broad tumoral non-invasive meningiomas, interface with intervening leptomeningeal layer in brain invasive examples have an irregular border with finger-like tumoral projections into the adjacent brain parenchyma . Hypercellularity is a more diffuse accumulation of small cells, whereas macronucleoli are large enough to be visualized proper magnification. These 4 features likely reflect a loss of cellular differentiation, whereas the fifth criterion of spontaneous (non-embolization induced) necrosis suggests superimposed hypoxia. Micronecrosis with pseudopalisading is probably the most meaningful pattern of necrosis, since it has the strongest association with recurrence (Fig. 10 & 11).
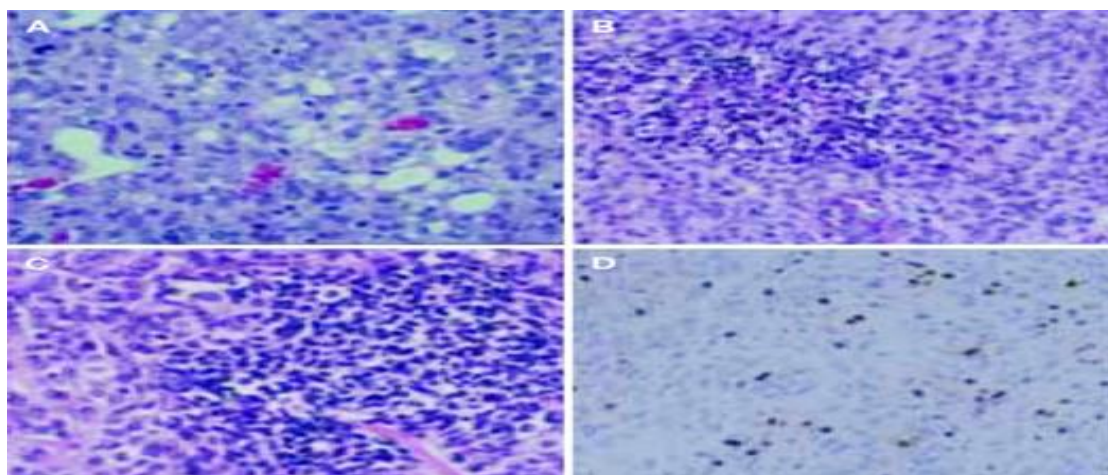

Figure 10A: Histopathological images (hematoxylin and eosin stain) of an atypical meningioma showing mitotic figures and macronuclei (A), sheeting and hypercellularity (with an area of necrosis) (B), small cell formation (C), and MIB-1 labeling (D).
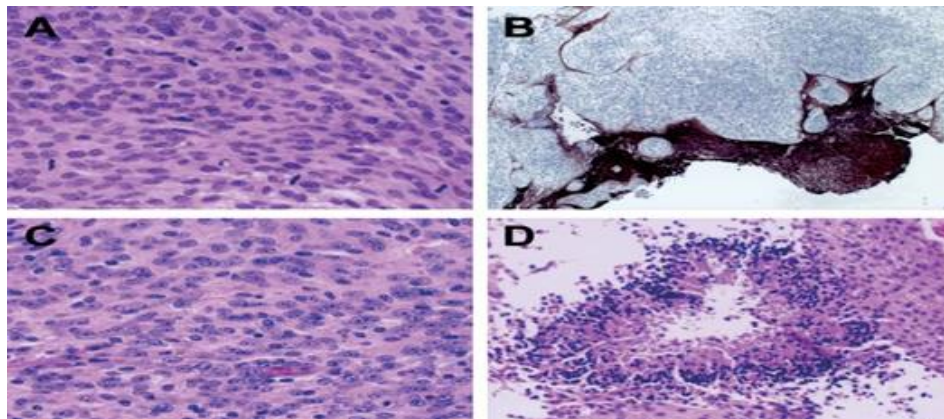
Figure 10B. Atypical (WHO grade II) meningiomas with: (A) Frequent mitoses despite bland cytology; (B) Brain invasion with entrapped intratumoral fragments of GFAP-positive brain tissue; (C) Two dimensional sheeting and macronucleoli; (D) Focus of micronecrosis with pseudopalisading.

3.5 ANAPLASTIC (MALIGNANT) MENINGIOMA, WHO III:

Anaplastic or malignant meningiomas are rare, highly aggressive tumors, accounting for only 1– 2% of resected cases. They represent greater degrees of cell cycle deregulation and loss of differentiation with focal or diffuse findings of excessive mitotic index (>20/10 HPF) and/or frank anaplasia. This latter criterion is rather subjective, currently defined as sarcoma, carcinoma, or melanoma-like morphology (Fig. 11 - 13). In other words, frankly anaplastic foci are difficult to recognize as being meningothelial in origin and when diffuse, may require immunohistochemistry, electron microscopy, or even genetic studies for confirmation. [16, 19, 20-34, 39-52, 56-67, 69-79, 89-115, 119, 125-131, 133, 141-146, 155-159, 162].
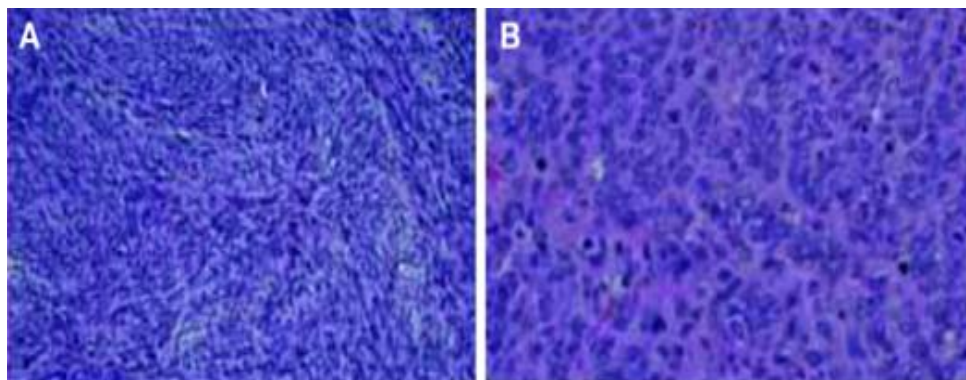

Figure 11A: Histopathological images (hematoxylin and eosin stain) of an anaplastic meningioma showing sarcoma-like morphology (A) and mitotic figures (B).
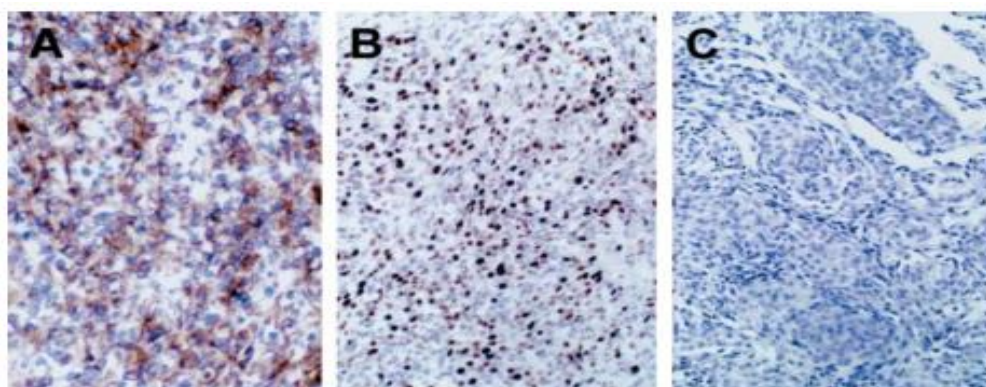

Figure 11B: Immunohistochemistry in an anaplastic meningioma showing patchy EMA immunoreactivity (A), markedly elevated MIB-1 (Ki-67) proliferative labeling index (B), and lack of PR staining (C).

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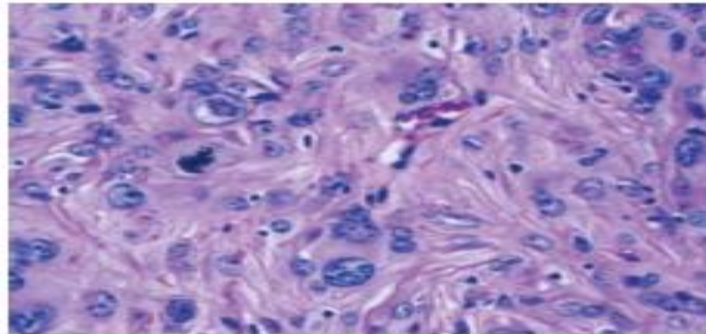
Figure 11C: Anaplastic (malignant) meningioma (WHO grade III) with cytologic anaplasia, such that the meningothelial derivation is no longer recognizable.

Most display patchy EMA immunoreactivity, a high proliferative index, and lack of progesterone receptor (PR) expression (Fig. 8 - 12). They may present either apparently de novo or following one or more recurrences of lower grade meningiomas (malignant progression). The median overall survival is less than 2 years. (See Fig. 8 - 12). [12, 16, 19, 22, 25-33, 45, 56, 67, 77, 89-119, 123-135, 141-148, 155-159, 161-162].

3.6 DURAL SPREAD, CLONALITY, AND MULTIPLE MENINGIOMAS:

The finding of non-familial multifocal meningiomas is relatively common, encountered in roughly 3% of patients from surgical series and 8% from autopsy series. Potential explanations include: (a) a field effect with genetic [e.g., germline mutation of the neurofibromatosis type 2 gene (NF2) orNF2 somatic mosaicism] and/or environmental factors (e.g., ionizing radiation) predisposing large areas of the meninges towards neoplastic transformation leading to polyclonal tumor development, or (b) seemingly separate dural-based deposits derived from a single parent tumor (i.e., a monoclonal process). Data suggest that in fact, both occur. [20, 23, 44-49, 52-58, 66-69, 76-79, 83-101].

For instance, in a study of 39 meningiomas derived from 12 non-NF2 patients with multiple meningiomas, Stangl et al. found that 6 of 10 informative cases had identical NF2 gene mutations in all meningiomas derived from the same patient. In other words, over half the cases were monoclonal, despite multifocal localization. The authors suggested CSF spread as a possible mechanism, though this seems unlikely given the lack of drop metastases or a neoplastic meningitis pattern. Instead, it is common in meningiomas to see some intradural spread radiating away from the point of dural attachment, sometimes in a discontinuous fashion. An intradural mechanism of invasion and migration is therefore suggested and further supported by data from Borovich and Doron, who uniformly found meningothelial nests in radial strips of dura adjacent to meningiomas, but not in control samples of dura from the convexity. On the one hand, this may explain the surprising finding of recurrences in benign meningiomas that were previously felt to be completely resected. However, it is also suggests that multifocal meningiomas may arise from widespread intradural spread with tumor deposits growing beyond the proximate region surrounding the parent neoplasm. Meningiomas have enhanced invasive and migratory capabilities, despite an often benign histology. On the other hand, it has also been reported that some solitary meningiomas are polyclonal, perhaps suggesting that there is some blurring of the lines between meningothelial hyperplasia and neoplasia.
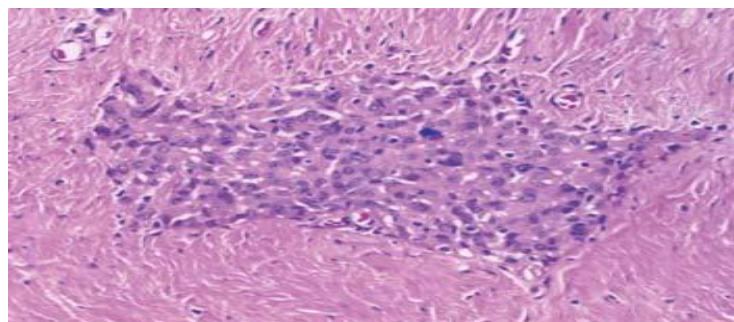

Figure 12: Microscopic nest of tumor cells in sampled dural strip, consistent with dural invasion and migration by this otherwise benign-appearing meningioma.

3.7 CEREBRAL EDEMA:

It is well known that the morbidity and mortality associated with meningiomas is not only due to the mass effect created by the tumor itself, but also the peritumoral cerebral edema associated with it. Psychiatric symptoms have been specifically correlated with increased edema, particularly in frontal lobe meningiomas. The presence or absence of peritumoral edema and its extent are highly variable and greater degrees of edema have been associated with large tumor size, parasitization of pial vasculature, convexity/middle fossa localization, irregular tumor–brain interface, hyperintensity on T2-weighted images, brain invasion, high grade, and secretory, microcystic and/or angiomatous variants. Some have suggested that increased VEGF expression is associated with edema. [18-39].

3.8 BONE INVASION AND HYPEROSTOSIS:

Bone invasion is common in meningiomas, particularly those at the skull base. Although osteolytic lesions may also be seen, hyperostosis is more typical and nearly always signifies bone invasion. It has been suggested that meningiomas secrete osteoblast stimulating factors, with alkaline phosphatase as one potential candidate, since it is often increased in tumors with hyperostosis and/or numerous psammoma bodies. Other possibilities include PDGF, IGF1, IGF2, FGF, and TGF. Dural, soft tissue, and brain invasion had given the often invasive nature of meningiomas, it is not surprising that alterations in the regulation of extracellular matrix (ECM) proteins have been found, including overexpression of matrix metalloproteinases, such as Matrix-Metalloproteinase MMP-9 and MMP-2. Other ECM-associated proteins, e.g., SPARC, tenascin, and sromelysin-3, have been correlated with increased invasiveness. As stated earlier, brain invasion reflects a more aggressive biologic potential. The molecular explanation for the ability to penetrate the pia has yet to be determined. [28-39, 44-68, 78, 105].

3.9 IMMUNOHISTOCHEMISTRY AND GROWTH KINETICS:

Meningiomas have been extensively studied with immunohistochemistry, though most markers have not been shown to have diagnostic or prognostic relevance. There are few reliable antibodies in common clinical use today and additional ones are sorely needed. Currently, the most reliable marker is EMA, with immunoreactivity in 50–100% of meningiomas, including anaplastic cases. Unfortunately, it is often weak and patchy and since most laboratories titer their EMA controls for the high levels of expression in carcinomas, it may be necessary to use a higher antibody concentration for optimal sensitivities in meningiomas. Other membrane and intercellular junction-associated candidates, such as E-Cadherin, Neuron-Specific Enolase (NSE), Protein S-100, Desmin, HNK-1 (Leu-7), Claudin, Desmoplakin, and Connexin were utilized in research, but are not yet common in clinical settings. Vimentin is typically strongly and diffusely positive, though this has poor specificity. [15, 19, 32-44, 119]

Similarly, prostaglandin D synthase (PGDS) is a major CSF protein component chiefly synthesized by meningothelial cells and thus, represents a promising potential marker of meningothelial origin. A recent study revealed immunoreactivity in 80% meningiomas, with other CNS and soft tissue tumors generally lacking expression, though surprisingly, 64% of meningeal hemangiopericytomas were also positive. [8, 41, 111].

Prognostically, proliferative markers have been useful, particularly MIB-1, which is used in clinical applications to determine the Ki-67 labelling index and is applicable to paraffin sections. Ki-67 and MIB-1 monoclonal antibodies are directed against different epitopes of the same proliferation-related antigen. Ki-67 and MIB1 may be used on fixed sections. In case of infiltration of brain tissue by the tumor, GFAP marker can determine the not affected glial cell formation and then a distinguishing from tumor tissue can be achieved. (Meis et al., 1986, Chronwall et al., 1983). Approximately 64% of all meningiomas have positivity of expression of progesterone receptors. Whether or not elevated indices represent an independent prognostic variable has been debated though, since they increase proportionally to both ordinary mitotic counts and histologic grade in general. Another major problem is the inter-laboratory variability in staining and interpretation, making it difficult to extrapolate cutoffs from one study to another. Nonetheless, MIB-1 and PR immunostains may both be useful in borderline atypical or borderline anaplastic meningiomas. Data by Nakasu et al. further suggest that very focal elevations in the proliferative index may not be as significant as more diffuse ones.

3.10 METASTASES:

This is a rare feature, even for anaplastic meningiomas. Thomas et. Leonetti (1994) reported about metastases of papillary meningiomas with mostly hepatic, bony and pulmonal (Pasquier et al, 1986, Avninder et al 2007). Benign meningiomas can also spread to other locations, including within the craniospinal axis and into CNS tissue.

4. PREDISPOSING FACTORS

4.1 FEMALE GENDER AND HORMONE RECEPTORS:

Based on the significant female predilection for meningiomas and the fact that some of them grow during pregnancy or during the luteal phase of the menstrual cycle, a tumorigenic role for hormones has long been suspected. A number of steroidal and non-steroidal hormone receptors have been detected in meningiomas, the best established of which is the PR. Although one might expect these receptors to be limited to sexually mature women, they are also detected in men and children, suggesting that their role in pathogenesis is not that simple. Nevertheless, support for PR activation in meningiomas comes from the fact, that normal arachnoidal cells express very little of this receptor, progesterone stimulates in vitro growth of some meningioma cell lines, and PR antagonists inhibit growth of some cell lines. Interestingly, PR expression is roughly inversely proportional to both tumor proliferation and histologic grade, such that the greatest likelihood of immunoreactivity is in the benign examples (50–80%). Meningiomas express little estrogen receptor (ER), suggesting that as opposed to breast cancer, another hormonally driven neoplasm, PR expression is not regulated in an estrogen dependent manner. Although a mutant form of ER has been found, it similarly does not appear to regulate PR synthesis in meningiomas. Clinical trials utilizing antiprogestational agents have unfortunately been disappointing to date, perhaps because the meningiomas in greatest need of adjuvant therapy (e.g., high-grade) are least likely to express PR. Other receptors commonly detected in meningiomas include androgen, somatostatin, growth hormone, and prolactin receptors. Their precise biologic roles have yet to be determined. [1].

4.2 NEUROFIBROMATOSIS TYPE 2 (NF2) / OTHER MENINGIOMA SYNDROMES:

NF2 is a genetic disease characterized by frequent CNS tumors. As part of Knudson's two-hit hypothesis, one would predict that familial tumors with germline mutations should present at an earlier age than their sporadic counterparts because every cell in the body already has one of the two gene copies inactivated. This scenario appears to hold true with the NF2 gene. After vestibular schwannoma, the next most common tumor type in NF2 is meningioma, encountered in roughly half of cases [82-112]. Furthermore, the severe 'Wishart' variant is more likely to present with pediatric meningioma as the first manifestation of disease. Therefore, it is not surprising that approximately 40% of children with meningiomas have NF2. In terms of other genetic syndromes predisposing to meningiomas, none have been firmly established, though there are rare examples of familial non-NF2-associated meningiomas. Such cases suggest that other tumor suppressor genes may be involved. One familial example was characterized specifically by clear cell meningiomas. Rare meningiomas have also been reported in patients with Cowden's syndrome, Gorlin's nevoid basal cell syndrome, Li-Fraumeni syndrome, Turcot's/Gardener's syndrome, and von Hippel-Lindau disease [60-69]. It has yet to be determined whether these associations are causal or coincidental, though it is of interest that a VHL gene mutation was recently described in a meningioma from a patient with von Hippel-Lindau disease.

4.3 MENINGIOMA WITH MENINGIOANGIOMATOSIS:

Meningioangiomatosis (MA) is an enigmatic cortical and leptomeningeal mass lesion, encountered either sporadically or in the setting of NF2. It is thought to be hamartomatous or reactive in nature and is characterized by a perivascular spindle-cell proliferation of presumed meningothelial origin, based on the presence of psammoma bodies, occasional EMA immunoreactivity, and the coexistence of an adjacent meningioma in some cases. It has been speculated that such meningiomas arise as a result of neoplastic transformation in a perivascular meningothelial cell within the MA. [149-175]

However, recently a case with identical genetic alterations was encountered in both the MA and meningioma components, suggesting the alternate possibility that meningiomas may occasionally spread extensively along perivascular spaces, thus mimicking the architectural pattern of MA. In fact, the resemblance of MA to brain invasion has been previously emphasized, with a cautionary note against overgrading in this setting. [1-17, 19-41, 46-73, 82-98, 101-111, 129-139]

4.4 SECRETORY MENINGIOMAS (SM):

SMs are a benign meningiomas subtype. Intratumoral calcification or cystic changes were scarcely observed in SMs. Preferred cranial base locations, typical hypo- to iso-signal in T1 weighted, hyper-signal in T2 weighted MR images and "xenon light"-like enhancement could make preoperative diagnosis of SMs probable. (See Fig. 13). PTBE in SMs

correlated with irregular margin, absence of peri-tumoral rim and non-cranial base locations. [160-165] A 100% CEA, CK and PR positivity was seen in many cases that had available data. The prognosis of SMs is comparatively good, as a slow-growing benign tumor. Patients' outcome is associated with surgical risks and extent of tumor resection, rather than the extent of PTBE. Cranial base SMs were more risky for surgical procedure and were often given incomplete tumor resection, hence had worse short-term and long-term prognosis than non-cranial base SMs. Residual operated SMs grew slowly, which reacted quite well to radiation therapy.
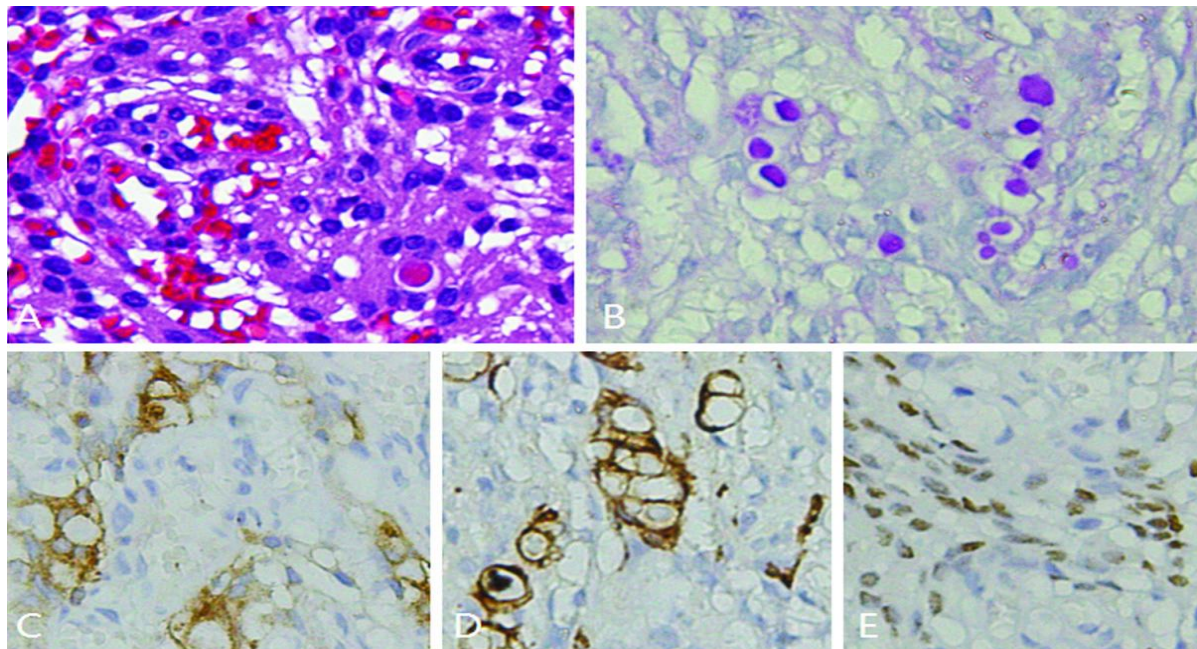

Figure 13: Immuno-histochemical features of a secretory meningioma (case 65). A: Abundant pseudopsammoma bodies shown on H&E sections; B: PAS stain; C: Labeling of CEA; D: Labeling of CK; E: Labeling of PR. Original magnification: ×400 for all sections.

4.5 RADIATION-INDUCED MENINGIOMAS:

Besides NF2, the other well-established predisposing variable in meningiomas is ionizing radiation. Ironically, radiation also represents the only currently accepted adjuvant therapy for cases that are recurrent, clinically aggressive, or have failed surgical therapy. The vast majority of patients with post-radiation meningiomas have received their radiation exposure during childhood. It has been estimated that the relative risk for the development of a subsequent meningioma in children receiving low-dose cranial irradiation is nearly 10-fold over those without such exposure, suggesting that there may be a critical window of susceptibility during childhood for neoplastic transformation of meningothelial cells by radiation. Support for this hypothesis comes from reports of a significant increase in the incidence of meningiomas in Israel after the widespread use of low-dose scalp irradiation to treat children with tinea capitis in the 1950s. The average latency period has been reported as 11–43 years after irradiation. There is some debate regarding whether or not radiation-induced meningiomas are more likely to be malignant. Our anecdotal experience is that indeed a higher proportion are aggressive, but the issue remains difficult to resolve, since most published series have not applied current grading criteria and the clinic-pathologic data is often incomplete.

Nonetheless, radiation-induced meningiomas typically present at an earlier age, arise within the prior irradiation field by definition, and are more likely to be multifocal. Histologic findings in radiation-induced meningiomas include high cellularity, marked pleomorphism/atypia with numerous giant cells, vacuolated nuclei, vascular hyalinization, and increased mitotic activity. However, none of these features are absolutely specific and any or all may be encountered in meningiomas unassociated with prior irradiation, albeit less often. Genetic studies have shown that the NF2 gene is less often implicated in radiation-induced than in sporadic meningiomas. Instead, there are often complex structural and numerical chromosomal abnormalities. A specific genetic signature has not been identified [70-75, 77, 99-114]. (See Fig. 14)
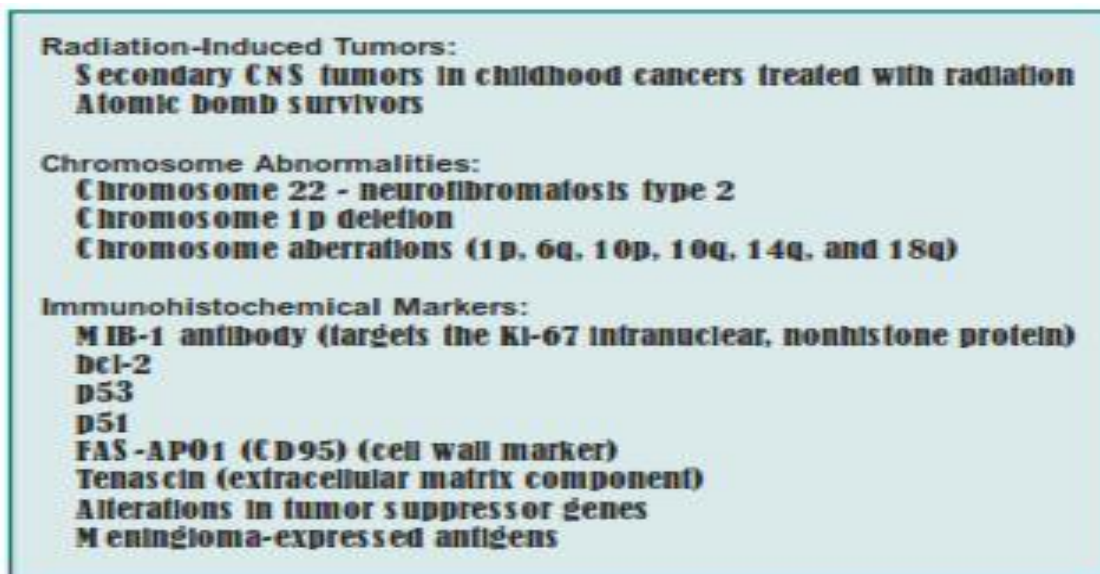
Figure 14: Predictors of Refractory Meningiomas.

However, Zattara-Cannoni et al. recently described a characteristic derivative chromosome 1 in six radiation-induced meningiomas, suggesting that a region on 1p13 may be critical to the development of these meningiomas.

5. GENETICS

5.1 GENERAL CONSIDERATIONS:

Loss of genetic material at chromosome 22q12, between the myoglobin and the c-sis proto-oncogene loci, has been reported to lead to the initiation of a meningioma. This area represents a tumor suppressor gene. Both alleles must be affected before an arachnoid cap cell might turn into a meningioma. The protein encoded by this gene, known as Merlin or Schwannomin[102-119] is a structural protein located in plasma membranes that links the cytoskeleton to the cytoplasmic membrane. This is the same genetic locus that is abnormal in NF2. Loss of Merlin leads to a loss in cell polarity, increased motility and invasiveness, and reduced contact inhibition, but the mechanism by which it exerts a tumor suppressive effect is not completely understood. Benign meningiomas are monoclonal; up to 70% can have the 22q12 mutation. Other mutations at 18p11 and 1p35 are also found in benign meningiomas. With accumulation of further mutations, they can become atypical and then anaplastic. Loss or increase of alleles results in this malignant progression. This can take place de novo in a meningioma, or it can occur during recurrence. In 1997, Weber et al. 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 then 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 a loss on 9p (the CDKN2A, CDKN2B, and ARF genes) resulted in an anaplastic tumor. The only specific abnormal known genes are the NF2 gene and the CDKN2A, CDKN2B, and ARF genes. The latter three on 9p are involved in the G1/S phase cell cycle checkpoint. It is not known what genes are abnormal on the other chromosomes that have mutated. (See Fig. 14 & 15). This theory of malignant progression is supported by the fact that benign meningiomas can recur with atypical or anaplastic pathology. Other tumors, such as gliomas, have been shown to mutate into malignant forms from an originally "low-grade" lesion after accumulating genetic abnormalities. However, Al-Mefty et al. (2004, 2010, 2014) attempted to follow pathological malignant progression in recurrent meningiomas and found that the genetic alterations in the tumor cells were already apparent in the benign meningioma state. Thus, their results contradict the stepwise progression of genetic alterations described previously, but they only studied four specimens, and only three chromosomes were analyzed: chromosome 1, 14, and 22. Cytogenetic analysis of radiation-induced tumors does not reveal these typical chromosomal changes; these tumors can have multiple complex chromosomal aberrations. Abnormalities in the NF2 gene or chromosome 22 are less consistent [164].

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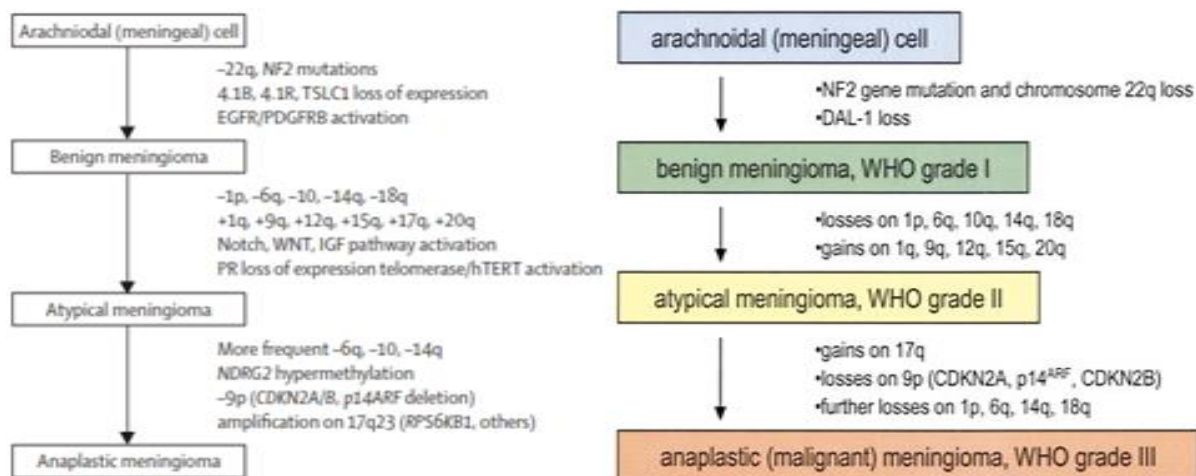
Figure 15: Hypothetic model of genomic alterations associated with the formation of benign meningiomas and progression towards atypia and anaplasia. Only those alterations that were found in more than 30% of tumors of a specific grade in the majority of studies (see text) are listed as contributing to the development of a particular grade (arrow). Alterations that increase in frequency by at least another 20% (averaged over several studies) in tumors of the next higher histological grade, despite already contributing to the previous grade, are listed again.

5.2 CYTOGENETIC AND MOLECULAR GENETICAL FEATURES:

5.2.1 Monosomy 22:

Meningioma was the first solid neoplasm associated with a characteristic cytogenetic alteration, that of monosomy 22. Subsequent data suggested that the NF2 gene was the primary target, with mutation and/or deletion constituting an early tumorigenic event in roughly half of sporadic and the majority of NF2-associated meningiomas (Fig. 14 & 15). Some authors have reported that NF2 inactivation is less common in meningothelial meningiomas than in transitional and fibrous meningiomas, particularly in the region of the anterior skull base. Lastly, genetic studies suggest that occasionally, other chromosome 22q loci besides NF2, including AP1B1/BAM22, MN1, and SMARCB1 (INI1/hSNFS) may play a role in meningioma [67-90, 93-117].

All tumors that retained the constitutional genotype on chromosome 22 also retained heterozygosity at all informative loci on other chromosomes analyzed, suggesting that the rearrangement of chromosome 22 is a primary event in the tumorigenesis of meningioma.

5.2.2 Monosomy of 1p chromosome and loss of ALPL function:

The complete activity loss of ALPL function and the immunologically detected loss of ALPL protein in areas of meningiomas with monosomy 1p indicate a cytogenetically undetectable inactivation of the homologous allele. Müller P et al. (1999) described deletion of chromosome 1p and loss of expression of ALPL, which indicates progression of meningiomas. The apparently homozygous loss of ALPL expression supports the notion that ALPL is a candidate tumor suppressor gene in meningiomas.

5.2.3 Protein 4.1 tumor suppressors:

The NF2 gene and its protein Merlin: One of the most frequently observed genetic alterations in meningioma is loss of heterozygosity (LOH) on chromosome 22q with bi-allelic inactivation of the NF2 tumor suppressor gene [39-52, 90-122]. Loss of NF2 gene expression is observed in all NF2-associated meningiomas and 40–60% of sporadic meningiomas. The NF2 gene encodes a protein, termed either Merlin or Schwannomin, with an open reading frame of 1785 nucleotides or 595 amino acids. Analysis of the predicted amino acid sequence demonstrated sequence similarity of Merlin and members of the Protein 4.1 family, specifically ERM proteins: Ezrin, Radixin, and Moesin. [4-19]

5.2.4 DAL-1 – Another tumor suppression gene:

DAL1, and its gene product, protein 4.1B, are believed to be frequently involved in the initiation of meningiomas that do not contain mutations in the NF2 gene. DAL1 loss has been demonstrated in approximately 60 percent of sporadic meningiomas. (See Fig. 16 & 17).

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Protein structure analysis predicts that Merlin is composed of three major domains: an amino terminal region (N-term) from amino acid residues 1 to 313, a central alpha-helical domain from amino acid residues 314 to 478 and a unique carboxyl terminal region (C-term) from amino acid residues 479 to 595 (or 596 in the mouse). At the protein level, Merlin is expressed in vascular smooth muscle cells, brain, leptomeninges, and Schwann cells by Western immunoblotting and immunohistochemistry [19, 22, 35, 44-59, 68-79, 88-114, 116, 118-129, 131, 133-144, 147, 150-153, 155-164].
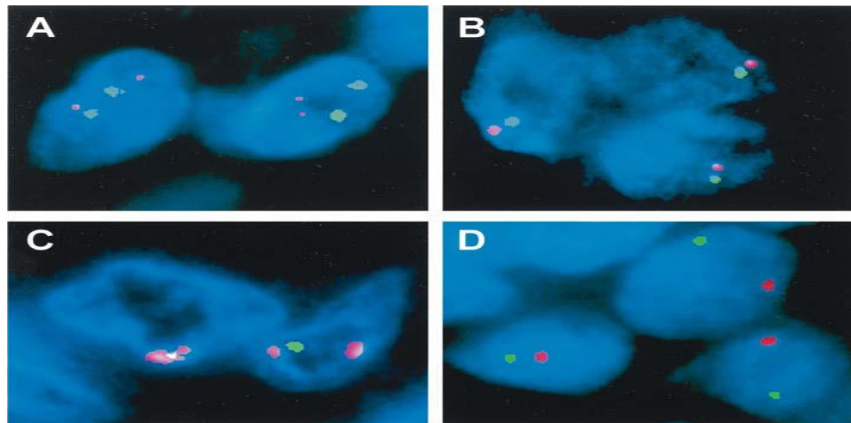

Figure 16: Common genetic patterns detected by FISH analyses in meningiomas. (A) Retained disomic (i.e., 2 copies) hybridization pattern for chromosome 22q (BCR on 22q11=green signals, NF2 on 22q12=red signals). (B) 22q deletion with only one green (BCR) and one red (NF2) signal per nucleus. (C) Deletion of Protein 4. 1B gene on 18p11 (green signals) with retention of both chromosome 18 centromeres (red signals). (D) Codeletion of chromosomal regions 1p32 (green) and 14q32 (red) in an anaplastic meningioma.
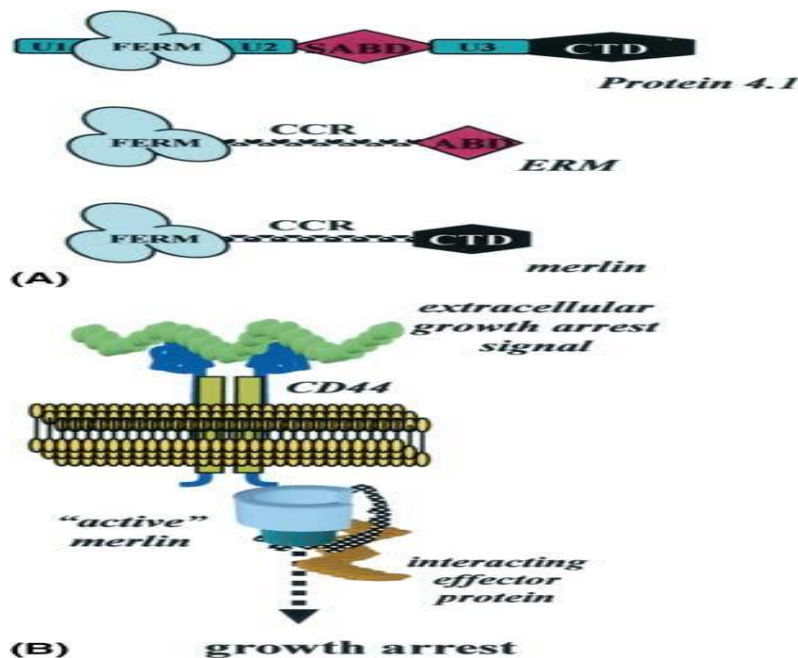

Figure 17: Structure and potential function of Protein 4.1 tumor suppressors. (A) The neurofibromatosis 2 (NF2) tumor suppressor (Merlin/Schwannomin) belongs to a structurally similar family of molecules that includes Protein 4.1 molecules (4.1R and 4.1B) and the ERM proteins (ezrin, radixin, and moesin). Each of these proteins contains a FERM domain (Four. 1-ezrin–radixin–moesin), which promotes interactions with cell surface transmembrane proteins (CD44 or TSLC1) as well as a domain that mediates binding to the actin cytoskeleton (actin binding domain, ABD in ERM proteins and spectrin-actin binding domain, SABD in Protein 4.1 molecules). Merlin lacks a conventional ABD/SABD region, but binds spectrin and actin. Protein 4.1 molecules contain interspersed unique sequence (U1, U2, U3) while Merlin and 4.1 molecules contain unique carboxyl terminal domains (CTDs). (B) One possible mechanism for Protein 4.1 growth regulation involves the engagement of Protein 4.1 tumor suppressors at the cell surface in association with transmembrane proteins, like CD44 and TSLC1, and propagation of the growth arrest signal through downstream interacting effector proteins (e.g., HRS).

5.2.5 Merlin function:

Several lines of evidence support a role for Merlin in the regulation of cell growth and motility. First, loss of Merlin in mouse embryonic fibroblasts (MEFs) is associated with defects in both cell growth and motility. NF2-deficient fibroblasts and keratinocytes also exhibit increased cell proliferation and accelerated cell movement in vitro. Second, loss of Merlin expression in genetically engineered mice by gene targeting results in increased cell growth and tumor formation. In NF2$^{+/-}$ mice, a wide variety of malignant tumors develop upon loss of the wild type NF2 allele, including fibrosarcoma, adenocarcinoma, hepatocellular carcinoma, and osteosarcoma . Tissue-specific NF2 inactivation in Schwann cells using Cre-Lox technology results in Schwann cell hyperplasia and schwannoma development in vivo [35-47, 57-69, 80-112, 117-130, 146-156, 160-164].

In addition, NF2 inactivation in leptomeningeal cells results in meningioma formation in mice. Moreover, tumors arising in NF2$^{+/-}$ mice are highly motile and metastatic. Third, re-expression of wild type, but not mutant, Merlin in tumor cell lines results in reduced growth in vitro and in vivo as well as reduced cell motility. One unique property of Merlin is its ability to regulate cell growth under conditions of increased cell density. NF2-deficient MEFs reach high saturation densities and exhibit abnormalities in contact inhibition growth arrest. Similarly, regulated Merlin expression in RT4 rat schwannoma cells results in reduced cell growth, which is most prominent after cells reach confluence. This defect in contact inhibition-dependent growth arrest is reflected in the inability of NF2-deficient cells to form productive adherens junctions. Merlin has been shown to interact with several potentially important interacting proteins, including a sodium–hydrogen exchange regulatory factor (NHE-RF), bII-spectrin (Fodrin), hepatocyte growth factor-regulated tyrosine kinase substrate (HRS), Schwannomin interacting protein-1 (SCHIP-1), Paxillin, and other ERM proteins. Merlin also binds several transmembrane signaling proteins, including b1-integrin and CD44. CD44 is a hyaluronic acid receptor that binds ERM proteins through amino acid residues in its carboxyl terminal cytoplasmic tail domain. Hyaluronic acid was shown to promote proliferation and motility in some cells, suggesting that the association between Merlin and CD44 might influence growth regulation and motility. Merlin binds to CD44 under conditions that promote cell growth arrest, and Merlin growth suppression can be attenuated by interfering with Merlin binding to CD44 In this fashion, growth regulation by extracellular cues may be mediated by Merlin binding to cell surface transmembrane proteins, like CD44. While it is not clear how the Merlin growth regulatory signal is propagated, the Merlin interacting protein, HRS, may be required for mediating Merlin growth suppression. In addition to Merlin protein interactions, Merlin growth suppression is also regulated by protein phosphorylation. Merlin phosphorylation is associated with reduced intramolecular complex formation, altered subcellular distribution, and reduced binding to CD44 in vivo.

Recent studies have shown that Merlin phosphorylation at S518 impairs the ability of Merlin to reduce cell growth and motility in vitro [80-131].

5.2.6 Other protein 4.1 molecules as meningioma growth regulators:

Although traditionally thought to regulate cell shape, recent studies have implicated protein 4.1 molecules in growth regulation. The prototypic erythrocyte protein 4.1 molecule (4.1R) has been analyzed in brain tumors. Inactivation of the 4.1R gene on chromosome 1p36 has been observed in neuroblastoma and recently meningiomas. In addition to 4.1R, another protein 4.1 member, robustly expressed in brain (4.1B; originally termed DAL-1) was identified as a potential tumor suppressor in lung and breast carcinomas. Using multiple approaches, 4.1B loss was demonstrated in meningiomas. Several lines of evidence support the classification of 4.1B as a tumor suppressor. First, 4.1B deletions have been found by LOH and fluorescence in situ hybridization (FISH) in lung, brain, and breast tumors. Second, studies in tumor cell lines lacking 4.1B have shown significant growth suppression following 4.1B re-expression. Third, Northern and Western blot analyses of matched normal and tumor tissues showed that 4.1B mRNA was absent or decreased in over 50% of tumors. Despite multiple attempts however, 4.1B mutations have not been identified within the non-deleted allele. It is possible that epigenetic silencing (e.g., methylation) might be operative in protein 4.1deficient tumors, as has been shown for Merlin and 4.1R. Similar to Merlin, 4.1B and 4.1R interact with Fodrin and CD44, but do not interact with either HRS or SCHIP-1. Preliminary yeast two hybrid interaction cloning experiments have identified 14-3-3 as a unique 4.1B-specific interacting protein. The 14-3-3 families of proteins are important regulators of signal transduction, which have been implicated in the regulation of cell survival and apoptosis. Further studies will be required to determine the functional significance of 14-3-3 binding. Recently, 4.1B was found to bind to the cytoplasmic tail of a transmembrane

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protein with structural similarities to CD44. This transmembrane protein, termed tumor suppressor in lung cancer-1 (TSLC1), was originally identified as a gene deleted in non-small cell lung cancer (NSCLC). Two-hit inactivation of TSLCl by promoter methylation and gene deletion was observed in 40% of primary NSCLC tumors. In addition, restoration of TSLCl expression suppresses tumor formation by A549 cells in immunocompromised mice. TSLC1 also functions as a cell adhesion molecule, suggesting that 4.1B binding to TSLC1 might modulate not only cell growth, but also cell adhesion and motility. Further work is required to determine whether TSLC1 functions to initiate protein 4.1B growth suppression, as has been proposed for CD44 and Merlin [101-115, 118-134].

5.2.7 Progression-associated alterations:

A number of cytogenetic alterations are associated with meningioma progression and atypical or anaplastic histology, including the presence of dicentric or ring chromosomes, losses of chromosome arms 1p, 6q, 9p, 10, 14q, and 18q, as well as gains/amplifications on 1q, 9q, 12q, 15q, 17q and 20q (See Fig. 18). In large part, the relevant candidate genes remain a mystery.

Interestingly though, there is some evidence to suggest that 14q deletions are more common in histologically benign meningiomas that subsequently recur [126, 128, 131-149, 151, 155, 159, 161].
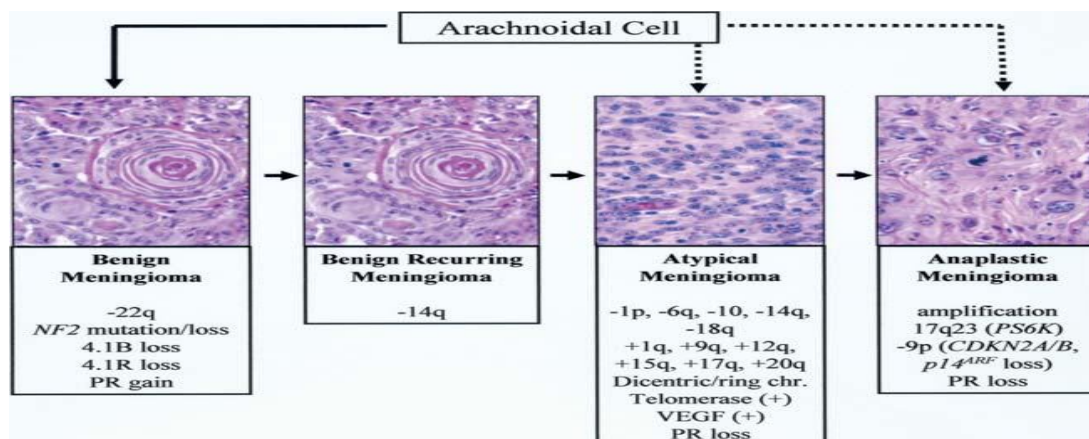

Figure 18: Current molecular model of meningioma tumorigenesis and malignant progression. The cell of origin is suspected to be either the arachnoidal cap cell or an earlier meningothelial progenitor cell. Progression from benign to atypical to anaplastic has been well documented, though direct transformation from a precursor cell to a more aggressive form of meningioma (dotted lines) is probably more common. Genetic alterations thought to be involved at each step are listed.

Alterations of the CDKN2A (pl6 [INK4a]), p14 [ARF], and CDKN2B (p[15INK4b]) tumor suppressor genes on 9p21 are associated with anaplastic meningiomas and found in about two thirds of the cases. Within the group of anaplastic meningiomas, patients whose tumors carry CDKN2A deletions have significantly shorter survival times as compared to patients whose tumors do not carry CDKN2A deletions. Mutations in the phosphatase and tensin homolog gene on chromosome 10 (PTEN, 10q23) or the cyclin-dependent kinase inhibitor 2c gene (CDKN2C, 1p32) have been detected in rare cases of atypical or anaplastic meningiomas, while amplification of the ribosomal protein S6 kinase gene (RPS6KB1, 17q23) has been found in a minor fraction of anaplastic meningiomas. High-throughput techniques such as gene expression profiling using oligonucleotide microarrays have provided the ability to screen thousands of genes simultaneously yielding additional gene candidates potentially involved in meningioma tumorigenesis and progression. The most biologically meaningful markers are likely to be those involved in critical cellular processes, such as angiogenesis, apoptosis, hypoxia, invasion, motility, growth, proliferation, and differentiation. For example, as a mechanism of bypassing cellular senescence in favor of immortalization, cells must maintain telomere lengths over multiple cycles of cell division, a process facilitated by the enzyme, telomerase. Apropos, telomerase activity has been associated with malignant progression in meningiomas. Tenascin, an ECM protein associated with invasion and angiogenesis, is also increased in advanced meningiomas. Similarly, VEGF was associated with malignant progression, in addition to increased vascularity and peritumoral edema. In terms of apoptosis regulation, it was shown, that Fas-APO1 (CD95), a tumor necrosis factor family member, is upregulated in malignant meningiomas. This is consistent with increased apoptotic indices encountered in these higher grade tumors [1, 4, 29-39, 41, 56]. (See Tables 3 and 4 above).

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5.2.8 Genetics of pediatric meningiomas:

Pediatric meningiomas and other meningeal tumors are uncommon and have recently been reviewed in detail. They are mostly encountered in the second decade of life, though they may occur at any age including infancy or even during fetal development. Unique aspects within this age group include higher frequencies of large tumor size, cyst formation, lack of dural attachment, high-grade histology, aggressive behavior, and aggressive variants, particularly the clear cell and papillary meningiomas. They are also more likely to present in unusual locations, such as lateral ventricles, posterior fossa, and spinal epidural regions. NF2 and prior irradiation are common predisposing factors and there is no female preponderance. Lastly, the biology of meningiomas is less predictable than in adults. Genetically, both sporadic and NF2-associated meningiomas shared with their adult counterparts, a high incidence of FISH detectable NF2 (22ql2) and Protein 4.1B (18p11.3) deletions, with corresponding losses of the protein products by immunohistochemistry. Similarly, Biegel et al. have demonstrated NF2 gene mutations in pediatric meningiomas, strongly implicating this gene in their pathogenesis. Lastly, pediatric meningiomas frequently have demonstrable 1p and 14q deletions, alterations generally associated with tumor progression in meningiomas [140-152, 159].

5.2.9 Growth factors and their receptors:

Literature regarding growth receptors and their downstream signaling pathways in meningiomas is often confusing due to challenges in elucidating their inter-relationships and determining which alterations are most critical. However, these pathways afford exciting opportunities to intervene pharmacologically with molecularly targeted therapy. Multiple autocrine and paracrine loops may be involved, one of the more common being overexpression of platelet derived growth factor BB (PDGF-BB) and its receptor (PDGFR-b). EGFR appears to be nearly universally expressed in meningiomas, but not in normal or reactive meningothelial cells. Its ligands, EGF and even more so, transforming growth factor alpha (TGF-a) are similarly expressed by tumor cells providing another potential autocrine loop. In contrast to glioblastomas, the EGFR gene is not amplified, suggesting alternate mechanisms for protein overexpression. Data further suggest that insulin-like growth factor II (IGF-II) and its receptor, IGF binding protein 2 (IGFBP2) also play an important role, with high IGF-II/IGFBP2 ratios associated with malignant progression. Expression of VEGF and its receptor have been primarily associated with tumor vascularity, peritumoral edema, and aggressive behavior. Likewise, endothelin 1 and its receptor, endothelin receptor type A have been implicated in angiogenesis and cell growth [19-32, 44, 49].

5.2.10 Cell lines and animal models:

A major hindrance to research in meningioma biology and therapeutic development has been the limited availability of robust cell lines and animal models. Obstacles have included the lack of animal models with sufficiently high frequencies of spontaneous meningioma development, challenges in establishing and maintaining viable *in vitro* and *in vivo* growth for otherwise benign meningiomas, difficulties in implanting intracranial dural-based tumors to accurately model the human condition, and lack of sufficiently meningeal-specific promoters for genetic manipulation. LTAg2B is the single human leptomeningeal cell line currently available, though immortalization by transfection with viral genes may have significantly altered the phenotype of these cells compared to ordinary non-neoplastic arachnoidal cells. The few human and rat meningioma cell lines that have been established are derived from malignant meningiomas and it is similarly difficult to know what types of culture-induced artifacts may be present. Most animal models have exploited xenografting into athymic mice, usually after culturing human tumor cells and inoculating them into extracranial sites. Therefore, the tumor grows in a very different environment than that encountered clinically. However, at least one intracranial approach has been reported [150-158, 160, 162]. Recently, a novel genetic model was devised utilizing Cre recombinase technology to specifically inactivate NF2 in arachnoidal cells, resulting in the formation of intracranial meningothelial hyperplasia and meningiomas in roughly 30% of the mice. This powerful new technology significantly improves on prior models and may open avenues of investigation never before possible in meningioma research.

6. DISCUSSION AND NOVEL TREATMENTS OF MENINGIOMAS

6.1 BASIC CONSIDERATIONS:

The incidence of Meningiomas, indicating of the population-based studies, is approximately 13-26% of all primary intracranial tumors. It has been estimated that the asymptomatic meningiomas account 2-3% of the population, although at some cases incidence approaches 6%. MRI study in the general population by Vernooij et al. (2007) reported a

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prevalence of 0,9%. Their occurrence increases with age (peaks after the fifth decade of life) and affects women more frequently with 2:1 female : male ratio. Contrary to commonly opinions, there is no evidence of an increased prevalence of meningiomas in cancer survivors. Spinal meningiomas represent 25-46% of spinal tumors, affecting more commonly middle-aged women and having thoracic laterality. Meningiomas most common arise from the arachnoid cap cells, optic nerve sheath, choroids plexus and rare from unknown and progenitor cells origin. According to WHO, they classified on the basis of the tissues involvement, dural site origin and histological type. The vast majority of spinal meningiomas have thoracic localization 80%, with benign behavior and intradural extramedullary lateral appearance, whereas in 15-27% of cases have anterior manifestation and their surgical removal is difficult. Meningiomas are the most common calcified intradural spinal tumors on CT scans and with low signal intensity on T2-weighted MRI associated with slower growth rate, but exhibit an uncommon totally ossification in only 1-5% of cases and more difficult resection than the usual type. Although meningioma is typically benign and slow growing in approximately 92%, appearing mostly in the later decades of life, they can be exhibit an anaplastic (1.0 to 2.8%) or atypical (4.7 to 7.2%) behavior, with 1,3 - 14,7% recurrence rate at the spinal cord meningiomas with more common appearance in men. While asymptomatic meningiomas are traditionally managed conservatively until symptoms develop or lesion growth occurs, it is likely that patients at high risk for symptom development – most common young people because of the higher growth potential, may benefit from earlier follow-up investigations, in order to decrease this possibility. Many measurements were useful to determine the extent of the increase of meningiomas, such as the calcification evidence on CT scans and T2-weighted MRI, the depending of patient's age to the decision of operation, the symptomatology and comorbidities. Furthermore, in surgical treatment of asymptomatic meningiomas, the morbidity rate was 4.4% in patients younger than 70 years of age and 9.4% in those 70 years of age or older. The "gold standard" for symptomatic patients, is the complete tumor resection, although in elderly population the complications are more frequent. Some studies proposed a stereotactic radiotherapy as an alternative method, with low toxicity and the lack of treatment-associated mortality. In order to reduce the surgical complications in more aged patients with symptomatic meningiomas, Caroli and Sacko et al. (2012) proposed a grading system to standardize the surgical indications. On the other hand, for subtotal resected and recurrent meningiomas, radiotherapy (conventional or stereotactic) may be proposed. When all treatments (surgery and radiotherapy) have failed; hormonal therapy or chemotherapy can be applied. In the current study we reviewed the available treatment modalities for meningioma treatment [15-29,160-165].

6.2 SURGERY:

Surgery constitutes the first choice of treatment, when meningiomas are symptomatic, with more radical excision, because of latest approaches. Thus, the use of dorsolateral approach for foramen magnum meningioma, retrosigmoidal for petroclival or skull base approach for giant anterior clinoidal meningioma, usually offer very good results. Furthermore, microsurgical operation has given grate results and an effective resection. The new imaging techniques also, allow a better preoperative planning. Meningiomas are well MR perfused tumors and 3D-CTA helps to avoid vascular events, during surgical removal of the tumor. Single Photon Emission Computed Tomography (SPECT) and MR-Spectroscopy can show a good differentiation between anaplastic and benign meningiomas and Computed Tomography Venography (CTV) can provide a significant assistance at meningiomas located close to the Superior Sagittal Sinus (SSS). Recurrence rate has very well established and have been showed a depending on tumor's WHO grade and the extent of resection by Simpson criteria.

Many meningiomas cannot be totally resected because of their involving with vital neural, vascular (central veins) structures or are en plaque. Parasagittal meningiomas constitute a challenge for the surgeon; mainly when they arise from the middle and posterior third of Superior Sagittal Sinus (SSS). If the sinus is partially or completely occluded, may be opened and a total tumor resection could be proposed, followed by venous reconstruction. Also, an alternative plan is the outside of sinus tumor excision and coagulation of remnants or the use of radiation treatment. The restore of flow, by venous reconstruction and maintenance of cortical veins, offer a very useful collateral drainage. For the different locations, there are diverse approaches reported in the literature.

The management of meningiomas in children includes aggressive gross-total resection as first choice initial treatment. Radiotherapy has no benefit as initial treatment. Subtotal resection or WHO grade III tumors are in need of close observation.

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In the elderly patients also, the decision for operating or not, is individual. Severe concomitant disease or high American Society of Anesthesiology (ASA) score advice not to undergo surgical therapy. For elderly patients or asymptomatic with anterolateral meningiomas of the foramen magnum, conservative treatment is the recommendation. Spinal meningiomas have more frequently intradural-extramedullar localization, with the majority of them to be extended laterally or posteriorly. Microsurgical techniques and MRI can be helpful for a better clinical outcome and early diagnosis. An approximately 15-27% of spinal meningiomas, have an anterior to the spinal cord position, with difficult exposure. In these challenging cases, can be used the transthoracic approach with a better tumor visualization, but is more invasive procedure and there is a need for vertebrectomy.

6.3 RADIATION THERAPY (RT):

RT is recommended as an additional therapy in malignant or atypical tumors, mainly if incomplete surgical excision is performed. Concerning atypical meningiomas, in same reports with gross total resected tumors without RT, the recurrence rate after 5 years was 28%. In patients with high-grade atypical meningiomas, adjuvant RT improves patients' survival, only if there was brain involvement.

The extent of resection, p53 overexpression, malignant progression, brain invasion and the adjuvant RT, constitute the prognostic factors for anaplastic meningioma. In benign meningioma adjuvant RT is then proposed, in case of delayed tumor growth and the reduces of likelihood for further surgery. (See Figure 21 below).

Furthermore, RT can be beneficial for high surgical risk or advanced age patients. Also, it can be helpful in cases with tumor located in eloquent or surgical inaccessible areas. High dose RT also, has a significant improvement in malignant meningioma. Most of the patients with Tentorial Fold (TF) meningioma (TFM), after a total resection, suffer of permanent morbidity. They should be treated with radiation therapy [67-81].

6.4 STEREOTACTIC RADIOSURGERY (SRS):

Stereotactic radiosurgery (SRS) Stereotactic radiosurgery (SRS) or Gamma Knife SRS constitute a supplementary and effective management to a surgery and conventional radiotherapy treatment, in patients with brain tumors. In order to limit the side effects of radiation, especially in meningiomas, SRS allows smaller doses of radiation, improving survival and tumor control. Either as initial or adjuvant therapy, SRS achieved a high rate tumor control (98% with WHO Grade I tumors, 50% in Grade II and 17% in Grade III tumors) and only in 5% after radiosurgery was necessary an extra resection. Results were better for small to medium-sized symptomatic and newly diagnosed or recurrent meningioma. The use of SRS in patients with recurrent or residual atypical and malignant meningiomas can improve survival, with 68% in 5-year local control rate in atypical meningioma. Three-dimensional conformal radiotherapy for atypical and anaplastic meningiomas produced 5-year actuarial local control rates of 38% and 52%, respectively. Furthermore, SRS is safe and effective treatment option for radio-induced meningioma such as typical ones. SRS is a good option for convexity, parasagittal, and falcine meningioma as a primary or adjuvant therapy. For parasagittal meningioma, SRS resulted in 60% 5-year control rates for recurrent and 93% for residual disease.

Gamma Knife and Cyber Knife surgery can be used safely in small, minimally symptomatic or growing Foramen Magnum Meningioma (FMM). It is also useful and safe to use in residual tumors, after microsurgical removal. In skull base meningioma, the 5-year actuarial control rate was 87% for typical meningioma, 49% for atypical and 0% for malignant lesions and the radiosurgery related complications occurred in 3% of patients. SRS provided effective tumor control in patients suffering cavernous sinus meningioma, but does not improve neuralgia, in most patients, while subtotal tumor resection does not reduce the effectiveness of the method.

The use of SRS in cerebellopontine angle (CPA) meningioma, is possible to preserve cranial nerve function. Gamma Knife radiosurgery shows satisfactory results in long-term disease control of benign meningioma, with very low local tumor failure and treatment toxicity. Other reports mentioned an 89% 5-year tumor control rate and 5% complication rate. On the other hand, the use of radiosurgery in non-benign meningiomas is not effective enough. Results are better for small meningioma under the condition of using higher doses and greater marginal.

Radiosurgery also, has been beneficial for the treatment of intradural spinal meningioma, with a reduction of radiographic recurrence evidence [166].

6.5 STEREOTACTIC FRACTIONED RADIOTHERAPY (SFRT):

Stereotactic Fractionated Radiotherapy (SFRT) is the treatment of choice, for optic nerve sheath meningiomas. It is a safe option with low morbidity and satisfactory long-term results. Furthermore, SFRT improves disease-free period after subtotal resection and offers excellent help in management of the skull base lesions, reducing post-surgical lesions of the optic nerve. The restricted radiation tolerance of the visual pathways lesions is a great challenge and SFRS improves or stabilize visual deficit, in 89% of cases. The use is more meaningful before severe visual problems settle. There are also reports, suggesting that multisession therapy can be an effective alternative to either surgery or radiotherapy for selected lesions immediately adjacent to short segments of the optic apparatus. A single-fraction SRS provides a high rate tumor control, in cases of benign intracranial meningioma. In 317 patients with intracranial meningioma, FSRS was used as primary treatment, after subtotal excision or biopsy and for recurrence disease. 4.5 years after SFRT, 22 patients (6.9%) had local tumor progression, depending of histology and tumor volume as prognostic factors. Linear accelerator (LINAC) fractionated RT using the multiple noncoplanar dynamic rotation conformal paradigms can be offered to patients with meningiomas at the anterior visual pathways, an alternative to surgery or a primary treatment, with results similar to those reported for other stereotactic RT techniques. Furthermore, LINAC is effective and safe method, with a relatively high local tumor control and low morbidity, at incompletely resected or recurrent malignant meningioma [167].

6.6 THE ROLE OF PROTON BEAM THERAPY:

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. and Noel et al. [10-19, 28-33] showed that a proton boost, combined with 60 Gy photon therapy, can improve survival and local control. The former study reported a 5-year survival rate of 89% for atypical tumors and 51% for anaplastic tumors. Although the results seem promising, proton beam therapy is not easily available, it is very expensive to set up, and there are implicit limits to the size of tumor that can be treated. This makes other modalities such as intensity modulated radiation therapy (IMRT) more practical [168].

6.7 INTENSITY-MODULATED RADIATION THERAPY (IMRT):

Combined Stereotactic Radiosurgery and FSRS are both equally safe and effective in the management of symptomatic Cavernous Sinus Meningiomas (CSMs). The development of 3D conformal radiation therapy (CFRT), where the high-dose suits the target and avoids normal tissues, has been improved the effectiveness of radiotherapy. IMRT is the most advanced form of CFRT. This technique is useful for irregularly shaped tumors and too large for stereotactic radiotherapy. For that reason meningiomas are an ideal candidate. A study that compared static Conformal Field (CF), IMRT and Dynamic Arcs (DA) for skull base meningioma, reported that IMRT was more effective when the target volume was larger than 25 cm^3, because of a limited normal tissue sparing into the brain stem or temporal lobe. IMRT is an effective method for treating meningiomas causing ophthalmologic deficits. Additionally, the toxicity is minimal. The use of IMRT to treat grade II meningiomas with total initial margins (CTV + PTV) ≤1 cm, demonstrates efficacy and low risk of marginal failure with reduced margins. In patients with skull base meningiomas IMRT leads to long-term tumor control with minimal side effects, but also with preservation of quality of life. Furthermore, IMPT has the potential to overcome the lack of a framework for skull base tumors. Carbon ion plans offered considerably better dose distributions than proton plans in IMPT, but the differences were not clinically significant with traditional dose recommendation concepts. In a study with complex-shaped meningiomas of the skull base (54.3% benign tumors, 9.6% atypical and 4.2% anaplastic) the use of IMRT as primary treatment or postoperative for residual disease and treatment after local recurrence, was an effective and safe cure modality for long-term local control. In 39.8% of the patients, neurologic deficits improved, and worsened or developed new symptoms in 6 patients. In a study where compared the effectiveness and limitations of Stereotactic Arc Therapy (SRS/T), Intensity-Modulated Radiotherapy (IMRT), Helical Tomotherapy (HT), cyberknife and Intensity Modulated Multiple Arc Therapy (AMOA), on patients with benign brain tumors, including 5 meningiomas, all techniques provided good organs at risk sparing. HT provided best combination of indices, and between AMOA and IMRT, target coverage was similar, but taking into account organs at risk, AMOA was considerably preferable [169-170].

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6.8 BRACHYTHERAPY:

Ware et al. (1996, 2007), from the University of California at San Francisco, reviewed a series of 22 patients with recurrent atypical or anaplastic meningiomas who were treated with surgery and brachytherapy. Recurrent tumor predicts a poor outcome, thus warranting aggressive management. Therefore, after safely resecting all removable tumor tissue, I-125 was implanted into the tumor bed. This study comprised an equal distribution of atypical and anaplastic tumors, with similar survival rates in both groups. The median freedom from progression in 15 patients (who were followed closely) was 10.4 months, whereas the median survival was 2.4 years for patients with both recurrent atypical and anaplastic lesions after brachytherapy. Of the patients, 27% had wound breakdown problems and 13% required repeated resection for recurrence, eventually determined to be radiation necrosis. These complications are similar to those reported by Ojemann et al. (2011) after stereotactic radiosurgery. Thus, brachytherapy may play a role in therapy, but further study and larger numbers of patients are required. This form of therapy is for salvage purposes and should only be used when the patient is no longer a candidate for further externally delivered radiation therapy [171].

6.9 CHEMOTHERAPY:

While strong evidence exists for the standard therapy of meningiomas, inclusive of surgery and/or radiation therapy, for those tumors which recur, progress or are inoperable, the optimal medical therapies are yet to be elucidated. Traditional chemotherapeutic agents are not very effective against meningiomas. Hormonal manipulation is also under review in cases with untreatable tumors or those which are inappropriate for surgery. A number of challenges are apparent with respect to the use of chemotherapy or targeted therapy for intracranial meningioma.

There is very limited published literature that provides persuasive proof from which to establish appropriate treatment and there are a small number of clinical trials for patients with recurrent meningioma. Improved understanding of the molecular mechanisms driving tumorigenesis and malignant transformation has resulted in the targeted development of more specific agents for chemotherapeutic intervention in patients with non resectable, aggressive, and malignant meningioma.

Some studies analyze potentials benefits from chemotherapeutics, including cytotoxic agents, biologic agents, targeted molecular and hormonal agents. Most data is about hydroxyurea and somatostatin, although further trials with combination and targeted molecular therapies are still underway.

Hydroxyurea is a modestly active agent against recurrent meningiomas and can induce long-term stabilization of disease in some patients. It has been used for untreatable tumors, large residual tumors, benign meningioma of the skull base or those involving the dural venous sinuses. On the other hand, in many reports mentioned a limited effect of this agent, in atypical or malignant recurrent meningiomas. As for malignant meningioma, after total or subtotal resection and RT, adjuvant chemotherapy with cyclophosphamide, Adriamicin and Vincristine (CAV), has been used, with very good outcome (median survival 5.3 years).

Further, combinations of Andriamycin[R] and Dacarbazine[R] or Isosfamide[R] and Mensa[R] provide a more effective treatment.

Mifepristone can be also performed for prolonged periods in patients with non resectable meningioma, but have been reported many side effects, such as an irregular vaginal bleeding, endometrial thickening and biochemical hypothyroidism.

Currently, novel therapeutic drugs that act on growth factor receptors on meningiomas and other tumors are being manufactured and tested. Platelet-derived growth factor (PDGF) subunits and their receptors; specifically PDGF-A, PDGF-B, and PDGF-receptor are expressed in meningioma. PDGF-BB and activated PDGF-receptor are overexpressed in meningiomas; this growth factor and its receptor augments C-Fos levels via an autocrine or paracrine loop. This in turn causes increased cell division and tumor proliferation. Furthermore, Yang and Xu [149] reported significantly more PDGF-BB and PDGF-receptor in atypical and anaplastic meningiomas than in benign ones. Thus, increased interation between these two molecules may contribute to more malignant meningiomas. An anti-PGDF compound could therefore be tested in the treatment of these tumors.

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 its receptor are also expressed in meningioma, where they play a role in angiogenesis. VEGF expression is increased 10-fold in anaplastic and 2-fold in atypical meningiomas compared with benign meningioma. Peritumoral edema and microvascular density correlate with VEGF expression. Both PDGF and epidermal growth factor (EGF) increase VEGF expression. Therefore, anti-VEGF, anti-EGF, or anti-PDGF compounds may help to control tumor proliferation by an anti-angiogenic property. Several angiogenesis inhibitors that inhibit VEGF or the VEGF receptor are available: ZD6474 (AstraZeneca, Wilmington, DE), PTK787 (Novartis Pharmaceuticals, East Hanover, NJ), AEE788 (Novartis), Avastin (Genentech, South San Francisco, CA), and IMC-1C11 (ImClone). All these drugs are currently being investigated. Two EGF receptor antagonists, Tarceva (OSI774) and Erlotinib (ZD1839), were studied by the North American Brain Tumor Consortium in phase one protocols. After safety is established, both anti-PDGF and anti-EGF compounds could be used in Phase 2 protocols in patients with atypical or anaplastic meningiomas that are resistant to other therapy. As of now, none of the chemotherapeutic drugs showed any convincing effect on atypical or anaplastic meningiomas [172]. (See Fig. 19).
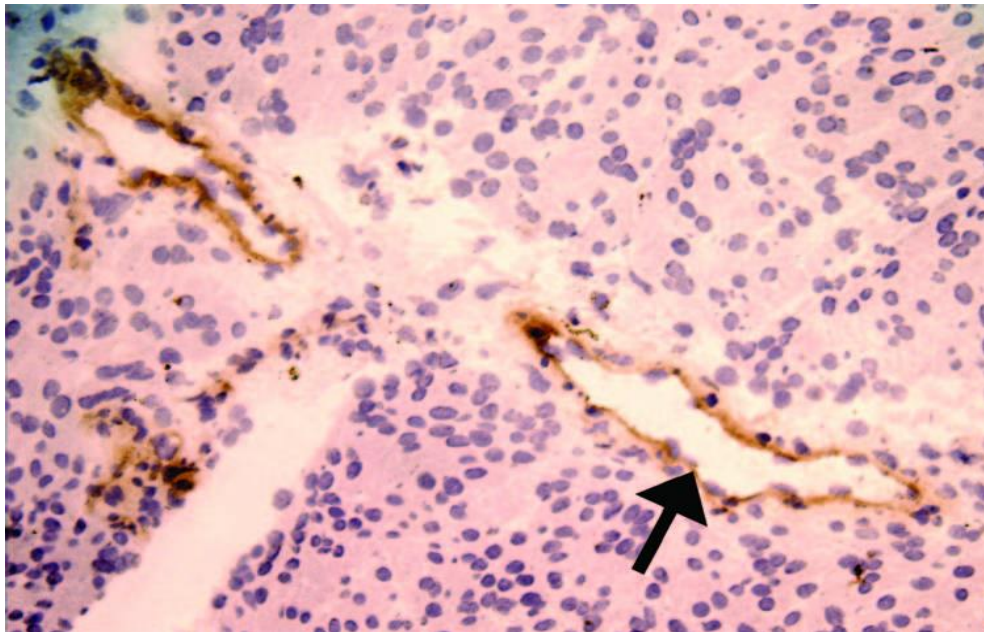

Figure 19: Atypical meningioma with vessel endothelium (arrow) showing strong immunohistochemical expression of VEGFR2 receptor (hematoxylin and eosin stain).

6.10 ENDOVASCULAR TREATMENT:

The rapid technological developments in endovascular materials, allowed a micro catheterization and embolization of meningioma. Angiography and more recently, selective intra-arterial injection of dilute MR contrast media, can be offer a better understanding and more clear view to the vascular blood supply of the meningioma. Furthermore, angiographic embolization reduces the need of transfusion during operation.

Embolization is recommended, in order to decrease the volume of the tumor and the surgical blood loss. Thus, may be beneficial in benign (Grade I) meningiomas, preventing the atypical histological changes, eliminating the postoperative complications and shortening the operative time. At inappropriate for surgery patients also, embolization can be used as an alternative treatment, with good results and tumor shrinkage in most cases.

On the other hand, the application or not of preoperative embolization in meningiomas, is still remaining controversial, due to the major complications, such as hemiparesis and tumor swelling. There are reports also, performed the used of the temporary clipping of external carotid artery, as an alternative (effective and safe) method for very large convexity, parasagittal and temporal base meningiomas. However, in patients whose tumor-feeding arteries run postero-medially toward the petrous apex or cavernous sinus is demanding more carefulness, since they are at increased risk of post-embolization cranial nerve palsy [173].

6.11 A PROPOSED TREATMENT ALGORITHM FOR ATYPICAL AND ANAPLASTIC MENINGIOMAS:

Although anaplastic meningiomas are more straightforward to manage, it is difficult to design a treatment algorithm for an atypical meningioma, because it really is a spectrum of disease. Management of these tumors at our institution is based on the Mayo Clinic pathological classification and corresponding prognosis and prognostic factors determined by Perry et al. [8-22, 30-49, 120-144]. All anaplastic meningiomas should be treated by FRT soon after resection. If there are focal nodular residual lesions amenable to treatment with SRS, it should also be considered. If there is a recurrence, surgical resection should be offered if possible. Further SRS for residual tumor is also an option. Atypical meningiomas that are subtotally resected should also be treated with early adjuvant FRT. Any focal nodular residual lesions could also be considered for SRS. If an atypical meningioma is completely excised but is found to be brain invasive, postoperative FRT is prescribed because nearly 60% of brain-invasive tumors recur within 5 years with an approximate 25% mortality rate.

When there is no brain invasion in an otherwise atypical meningioma that has been completely excised, other factors such as the number of mitoses and MIB-1 index are taken into account. With the minimal 4 mitoses/10 HPF, approximately half of the patients who have undergone gross total resection of a tumor will have recurrence at 5 years. It would seem reasonable to follow these patients closely without irradiation if the surgeon felt that the resection was truly excellent. If there are many more than 4 mitoses/10 HPF, this atypical meningioma is probably more aggressive and further treatment is based on judgment. (Fig. 20).

Study	MIB-1 LI Cut-Off Point	MIB-1 LI < Cut-Off	MIB-1 LI > Cut-Off
Korshunov[24] (2002)	4.4% (263 patients)	82% RFS at 6 yrs*	32% at 6 yrs*
Ho[22] (2002)	10% (83 patients)	100% RFS at 10 yrs (ie, no recurrence at 10 yrs [0/52])	3% RFS at 10 yrs (ie, 97% recurred within 10 yrs [30/31])
Nakasu[21] (2001)	2% (112 patients)	97% RFS at 10 yrs (ie, 3% recurred within 10 yrs [3/93])	57% RFS at 10 yrs (ie, 53% recurred within 10 yrs [10/19])
Perry[25] (1998)	4.2% (425 patients)	85% RFS at 7 yrs*	62% RFS at 7 yrs*

* Kaplan-Meier method
RFS = recurrence-free survival
LI = labeling indices

Figure 20: Comparison of Cut-Off Points for MIB-1 Labeling Indices in Predicting Recurrence Free Survival of Meningiomas Managed With Initial Gross Total Resection

Certainly, the recurrence rate for atypical tumors with 10, 15, or 19 mitoses / 10 HPF may be much greater than 50% at 5 years. Therefore, fractionated irradiation after gross total resection is reasonable. It is uncommon for pathologists to report the number of mitoses/10 HPF; therefore, the MIB-1 index is also used as an aid in determining management. If it is at least 4.2%, postoperative FRT is also offered. This leaves the gray zone of tumors that fall short of atypical meningioma criteria, those with bland histology and a MIB-1 index 4.2%, or those with perhaps a couple of histological features of atypia and, for example, 2 mitoses/10 HPF. (See Fig. 21 & 22). If such tumors are gross totally resected, it seems reasonable to watch them closely as well, and administer radiation therapy only after the tumor recurs. For the brain-invasive meningiomas that have no other characteristics of atypia and display pathological characteristics of chronic presence with gliosis (benign invasive meningiomas), further treatment may be based on the MIB-1 index after subtotal resection. If it is at least 4.2%, postoperative FRT is offered.

If totally excised, observation is acceptable. If meningiomas of any kind progress or recur after the above treatments, they should be operated again and excised if possible. Postoperatively, SRS can be used to treat any focal residual lesions. Patients who have not received before FRT can also be treated with this modality after surgery. Effective chemotherapy is currently not available.
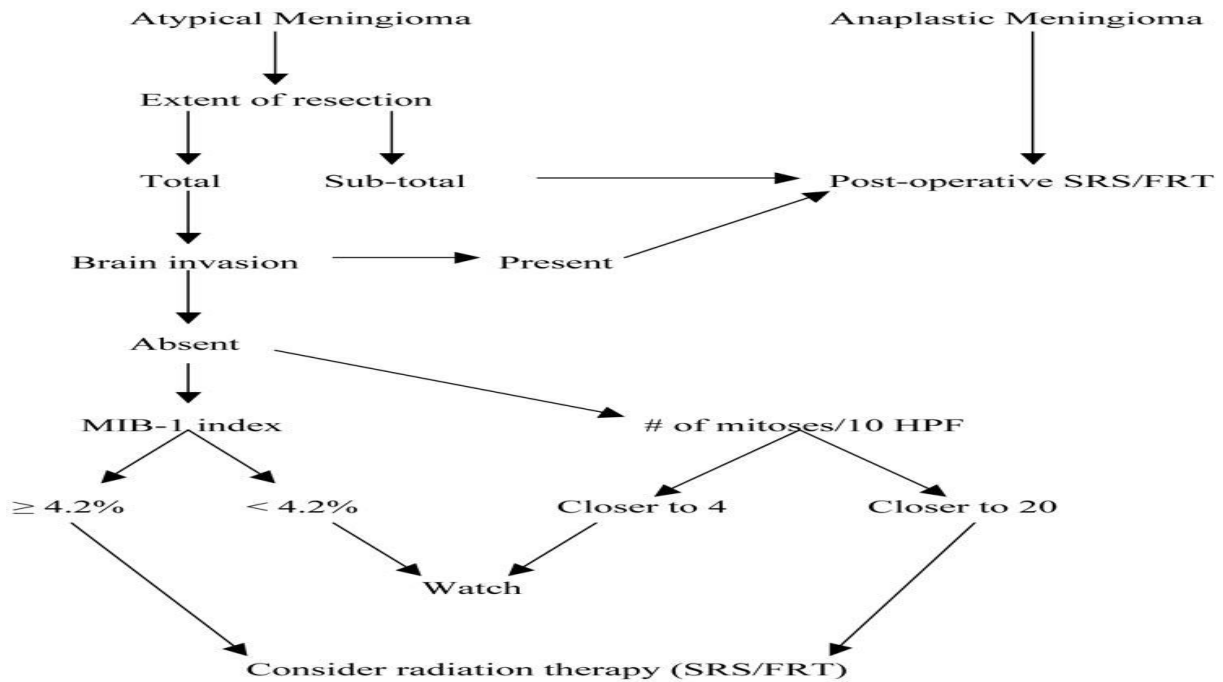
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Figure 21: Treatment algorithm for the management of atypical and anaplastic meningiomas.

6.11.1 Predictors of Refractory Meningiomas:

These tumors may prove difficult to be treated surgically or may respond poorly to radiation therapy. Location at the skull base, especially in the cavernous sinus, has a much higher recurrence rate than a tumor at the convexity. Other predictors of "difficult-to-treat" meningiomas include atomic bomb survivors, chromosome aberrations, and various histopathologic markers. Patients at increased risk for meningiomas include those who have had radiation exposure and those with NF2. Aberrations of 15-17 chromosomes were associated with higher-grade tumors include 1p, 6q, 10p, 10q, 14q, and 18q. Current researches on identifying specific markers (intracellular, cellular wall, or extracellular) that would identify recurrent meningiomas; of these, the MIB-1 antibody appears most promising.

Figure 22: Novel Treatment of Recurrent Meningiomas.

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Immunohistochemical staining with the MIB-1 antibody (Ki-67) has consistently correlated with meningioma recurrence.21-23 Ki-67 is a nuclear, non histone protein expressed during the proliferation phases of the cell cycle (G1, S, G2, M) and not expressed in the resting phase (G0). Staining with MIB-1 gives a labeling index (LI) that allows for quantification of the number of cells dividing. Santosh Saraf et al. (2011) recently studied 83 meningioma patients with total resections, who were followed for a minimum of 10 years. They report that 52 tumors had an MIB-1 LI <10%, and none of these recurred in 10 years. Of the 31 tumors with an LI >10%, 97% recurred within 10 years. Korshunov et al. (2002, 2011) stained 263 meningioma patients with the Ki-67 antibody and noted a significantly decreased recurrence-free survival in patients with an LI <4.4%. Variations between MIB-1 LI center around differences in tissue processing and the method of counting stained cells. An absolute value for the MIB-1 LI is difficult. Nakasu et al. **(Am J Surg Pathol. 2001 Apr; 25(4):472-8),** compared two methods of calculating the MIB-1 LI (area of highest labeling vs randomly selected) and concluded that a randomly selected method correlated better with meningioma recurrence. Other markers were reported to correlate with higher-grade meningiomas include the bcl-2 proto-oncogene, p53, p51, alterations in tumor suppressor genes, Fas-APO1 (CD95) transmembrane protein, the extracellular matrix protein Tenascin, and five novel meningioma-expressed antigens. These markers may provide in the future both identification of refractory meningiomas and "novel" therapeutic targets. Results of many studies indicated that MIB-1 LI and p53 protein expression were good indicators of histological grade in meningioma and may be particularly valuable for distinguishing borderline atypical meningiomas. Brain invasion is a prognostic parameter independent of grade, MIB-1 LI and p53 expression. [1-19, 42-77]

6.11.2 Current Treatments for Refractory Meningiomas / General Aspects:

The role of radiation therapy (RT) for the treatment of meningioma is still being defined. Irradiation of meningioma is frequently used for high-grade histology (atypical and malignant), high-risk locations (e.g., cavernous sinus), residual tumor, and patients who are poor surgical candidates. Studies have shown 5-year progression-free survival rates of 77% to 89% when fractionated external beam irradiation was used after subtotal resections in meningioma with typical histology. The use of stereotactic radiosurgery in the treatment of cavernous sinus meningioma reported a 5-year tumor control rate for typical meningioma of 93%. Overall, both conventional RT and focused stereotactic therapy have been shown to prolong the time until recurrence. Atypical and malignant meningiomas continue to be difficult to treat with any modality, including RT and stereotactic radiosurgery.

Hydroxyurea is a ribonucleotide reductase inhibitor commonly used in the treatment of hematologic malignancies. It diffuses into cells and inhibits DNA synthesis without interfering with RNA or protein synthesis by blocking the conversion of ribonucleotides to deoxyribonucleotides. Hydroxyurea was first reported to inhibit primary human meningioma cell growth in culture and in xenograft transplantation models. This drug was believed to be a powerful inhibitor of meningioma cell growth, most likely by causing apoptosis in the tumor cells. Recently, Rosenthal et al reported on 15 meningioma patients with residual tumor post resection and progressive growth, showing that 11 achieved stable disease with hydroxyurea. Mason et al. (2002) treated 20 documented enlarging meningioma (16 benign, 3 atypical, and 1 malignant) with hydroxyurea. 12 of the 16 benign tumors stabilized at a median duration of therapy of 122 weeks. The 4 remaining patients with benign tumors, as well as all of those who were diagnosed as atypical and malignant meningioma, and they had a progression of their disease. It appears that complete tumor regression is not a realistic goal with this drug. However, a reasonable number of patients have experienced tumor stabilization with minimal incidence of side effects after treatment with hydroxyurea. A current Southwestern Oncology Group Protocol in the USA (SWOG-S9811) is currently enrolling patients to further answer this question [175].

6.11.3 Mifepristone (RU486):

A discussion of the rationale of why hormone therapies are disappointing is beyond the scope of this paper. Briefly stated, numerous studies document that meningiomas are more common in women than men; also, the disease is exacerbated during pregnancy and menstruation, and both estrogen and progesterone receptors are found on meningioma. Olson et al. (1986) reported the initial activity of mifepristone (RU486) in tissue culture. Meningioma cell lines were derived from 3 patients, and all cells expressed estrogen and progesterone receptors. The use of RU486 inhibited growth of all 3 cell lines. These findings were confirmed by *both in vitro* and *in vivo* studies. 8 of 28 patients with meningiomas treated with RU486 experienced a "suggestion of response." In a separate clinical trial, 10 patients with 12 progressive recurrent

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and/or inoperable meningiomas were treated with a similar therapeutic regimen. Four tumors in 3 patients demonstrated tumor regression, 3patients had "stable disease," and 4 patients with 5 tumors had progressive disease. Prospective trials have been started, they appeared to be secondary to little response to treatment in the few patients studied. [39-52].

6.11.4 Novel Treatments for Refractory Meningiomas (RM):

Novel treatments for RM can be divided into several categories based on the underlying mechanism of action: angiogenesis inhibitors, inhibition of meningioma cell growth, blockade of growth hormone pathways, blockade of growth factor receptors, disruption of intracellular secondary pathways, and gene therapy (Table 5). (See chapters below).

6.11.5 Angiogenesis Inhibitors:

Tumors need to promote angiogenesis if they are to survive and grow. Inhibition of neovascularization is one potential strategy for treating hypervascular tumors. Interferon alpha (IFN-α), a leukocyte-produced cytokine, is a glycoprotein that is related to transforming growth factor beta (TGF-β) and tumor necrosis factor. The IFNs work mainly by their antiangiogenesis effect as well as by direct tumor cell inhibition. Interferon has been reported to have an effect on meningiomas *in vivo* and *in vitro*. Kaba et al. (2008) reported on 6 patients with recurrent or malignant meningiomas treated with IFN-α-2B. Five of the 6 patients had stabilization of disease progression, with the duration of tumor stabilization ranging from 6 to 14 months. Muhr et al. (1986, 1999) looked at meningioma metabolism in 12 patients treated with IFN-α. This group followed patients with serial [C]-L-methionine uptake positron emission tomography (PET) studies, and they showed stabilization of disease in 9 patients. They concluded that PET was a useful tool in determining responders to IFN treatment. In both reports, IFN treatment toxicities were tolerable, with patients complaining mostly of flu-like symptoms and leukopenia. Yazaki et al. (1995) looked at TNP-470, a synthetic analog of Fumagillin, and showed that it significantly inhibited tumor neovascularization and tumor growth of both nonmalignant and malignant meningiomas.

Endothelin (ET) is a peptide composed of 21 amino acids with three identified isoforms (ET-1, ET-2, and ET-3). They exert their effects via two receptor subtypes: ET-A and ET-B. Endothelins are angiogenic, potent vasoconstrictors (ET-A R) and vasodilators (ET-B R), and they also incite mitogenesis and c-Fos expression of neuronal cell types in vivo. Thus, ET has been hypothesized to promote angiogenesis and to act as an autocrine/paracrine growth factor in cerebral tumors. Harland et al. (2008) found that meningiomas expressed a higher level of ET-A receptors compared with normal cortex, and they concluded that the high affinity ET-A receptor antagonist PD156707 may be of therapeutic value in treating these lesions. [13-33, 111-132, 154-159, 172-176] Verotoxin has recently been studied as a new antineoplastic agent that targets the globotriaosyl ceramide (Gb3) glycolipid on tumor cells and tumor neovasculature. Verotoxins, or Shiga-like toxins, are produced by E. coli and are associated with the pathogenesis of hemolytic uremia syndrome, hemorrhagic colitis, and microangiopathies. Verotoxin is a type II ribosome-inactivating protein produced by pathogenic strains of E coli and targets only cells that express glycolipid, Gb3 (CD77). Gb3 was noted to be unregulated in many human cancers. The toxin consists of an A-subunit (enzyme) and B-subunit (antigen). The B subunit recognized specific glycolipids in particular cells known to be elevated in several human cancers. Al-Salhi et al. (2013) showed Verotoxin receptor was present in 9 (82%) of 11 malignant meningiomas and that intratumoral injection of Verotoxin in a mouse xenograft model resulted in increased survival of seeded animals. Microscopically, the Verotoxin-treated animals showed decreased microvascular density, increased apoptosis, and a decrease in meningioma cell proliferation.

6.11.6 Growth Hormone Inhibitors:

Interest in the roles that growth hormone (GH) and insulin-like growth factor I (IGF-I) in patients with acromegaly have a high incidence of meningioma (1.5% in one large series), and other studies showed involvement of IGF-I in meningioma growth in cultures. GH is produced and secreted from the anterior pituitary and stimulates the synthesis of IGF-I in the liver, the combined effects of which result in normal growth.

In vivo and *in vitro* studies showed that the GH-receptor is ubiquitous in meningiomas and that blockade results in decreased tumor growth.

Pegvisomant is a genetically engineered protein designed to be structurally similar to the natural human growth hormone. It is capable of binding to the growth hormone receptor, acting as a competitive antagonist. Friend et al. (2008) looked at 14 human meningioma specimens that were grown in primary culture. They found the ubiquitous expression of

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meningioma receptor mRNA in all 14 specimens, regardless of tumor grade (benign, anaplastic, or malignant). Blockade of the growth hormone receptor with Pegvisomant reduced serum induced DNA synthesis as measured by thymidine incorporation by 8% to 33% (mean 20%). IGF-I increased thymidine incorporation in primary meningioma cultures in a dose-dependent manner: 1 ng/mL, 5 ng/mL, and 10 ng/mL resulted in 21%, 43%, and 176%, respectively, above baseline. Based on the above study, McCutcheon et al. [161-162] took 15 human meningioma tumors and implanted them into the flanks of nude mice. They showed that after 8 weeks, the mean tumor volume of the group treated with Pegvisomant was 198.3 ± 18.9 mm^3 vs 350.1 ± 23.5 mm^3 for the control group (P<.001). The effects noted in this *in vivo* tumor model were most likely due to both the decrease in circulating IGF-I and the direct blockade of meningioma tumor growth hormone receptors. Furthermore, clinical trials have studied the treatment of acromegaly with Pegvisomant and have shown that this drug is well tolerated by patients. [159-162].

6.11.7 Somatostatin Agonist:

Somatostatin receptors are present on meningiomas in high density, and the addition of somatostatin in vitro inhibits meningioma cell proliferation.59,60 Schulz et al60 developed a panel of somatostatin receptor subtype-specific antibodies that showed a high expression of the sst2A subtype on 40 randomly selected meningiomas (29 [70%] of 40 meningiomas were ss2A positive). In contrast, all other somatostatin receptors were noted to stain weakly and sporadically. Based on these data, a prospective study of 16 surgically resected meningiomas was undertaken, and the level of sst2A expression was determined using Western blot analysis. The somatostatin sst2A subtype was readily detectable as a broad band migrating at Mr 70,000 in 12 (75%) of these 16 tumors; 8 tumors (50%) showed particularly high levels of immunoreactive sst2A receptors. There was an excellent correlation (P<.001) between the level of sst2A protein expression detected in Western blots and the sst2A-immunoreactive staining seen in tissue sections. The authors suggested that this immunohistochemical method could prove useful in identifying recurrent meningiomas that may respond to therapy with sst2-selective agonists. Garcia-Luna et al. reported on the clinical use of octreotide, a long-acting somatostatin agonist, in 3 patients with unresectable meningiomas. Doses used were gradually increased up to 1000, 900, and 1500 µg/24 hours during 16, 6, and 7 weeks, respectively. Patient tolerance to the drug was excellent, with abdominal discomfort and diarrhea observed in only 1 patient. Findings included the subjective improvement of headache in 2 patients and objective transient improvement in ocular movements in 1 patient. In all cases, computed tomography scans observed no change in meningioma size. This report confirms the safety of octreotide [48-61, 177].

6.11.8 Growth Factor Receptor Inhibitors:

The growth of human cerebral meningiomas in culture is increased by various growth factors, including epidermal growth factor (EGF), TGF-α and TGF-β, platelet-derived growth factor (PDGF)-BB, IGF-I and -II, and acidic and basic fibroblast growth factors. These factors may act in a paracrine and/or autocrine fashion to incite cell proliferation. Several studies have looked at disruption of growth-hormone-induced meningioma cell growth, including the growth hormone scavenger Suramin, the PDGF antagonist Trapidil^R, and inhibition of EGF-induced proliferation by Bromocriptine^R. Suramin scavenges exogenous growth factor, preventing the binding of a variety of growth factors to their receptors and inhibiting paracrine- and/or autocrine-mediated cell growth. Schrell et al. tested the ability of Suramin to inhibit growth-factor-induced meningioma proliferation in cell culture. They noted a 40% to 70% reduction in cellular proliferation and abolishment of growth factor-induced proliferation (EGF, IGF-I, and PDGF-BB) with the addition of suramin. Five tumor samples were studied using DNA flow cytometry. Suramin-arrested cells were observed in the S and G2/M phases of the cell cycle. Western blot analysis of 3 tumors showed a significant decrease in the amount of intracellular content of PDGF-BB after Suramin treatment. Suramin also prevented the binding of iodinated growth factors (ie, 125I-EGF, 125IIGF-I, and 125I-PDGF-BB) to their respective receptors. These findings prove that Suramin has the ability to inhibit autocrine loops (ie, lowering of intracellular PDGF-BB) and paracrine loops (ie, inhibiting cell growth). Suramin may control tumor proliferation in patients with recurrence. Meningioma cells secrete PDGF, which stimulates their own growth in an autocrine manner. Based on this finding, Trapidil^R, a drug known to have an antagonistic action against PDGF, was used to show a dose dependent inhibition of cultured meningioma cell proliferation in the absence of any exogenous mitogenic stimulation. The maximum effect was observed at a concentration of 100 µg / mL, with the decrease in cell growth ranging from 16% to 54% compared with control samples. Trapidil^R similarly inhibited the basal DNA synthesis assessed by [3H]-thymidine incorporation in 3 of 7 tumors. While the conditioned medium generated from meningioma cells remarkably stimulated the proliferation of tumor cells (166% to 277% of control), this effect was

strikingly inhibited by the addition of Trapidil^R. Trapidil^R also inhibited conditioned medium-stimulated DNA synthesis, even when there was no effect on basal DNA synthesis. Furthermore, Trapidil^R significantly inhibited the EGF-stimulated proliferation of meningioma cells. This inhibitory effect on EGF-stimulated cell demonstrates that Trapidil^R is not an antagonist specific to PDGF. The addition of Trapidil^R (30 µg/mL) in combination with Bromocriptine (1 µm) showed an additive inhibitory effect on the meningioma cell growth compared with montherapy alone. The overall results suggest that Trapidil^R exhibits an inhibitory effect on meningioma cell proliferation by blocking the mitogenic stimulation induced by autocrine or exogenous growth factors, and it may be considered as a possible new approach to the medical treatment of meningioma [178].

6.11.9 Signal Transduction Pathway Inhibition:

The growth of meningiomas in culture and the potent growth stimulation of meningioma cells by EGF and PDGF are inhibited by calcium channel antagonists. These studies arose out of the observation that calcium is an integral component of the intracellular signaling pathways. It was hypothesized that calcium channel antagonists might interrupt this signaling with subsequent growth inhibition. Interestingly, these studies and others concluded that the activity of the calcium channel antagonist agents had nothing to do with calcium signaling. Nevertheless, these studies were expanded into animal studies. A protocol was developed to allow for the growth of meningiomas in a xenograft model. Animals with subcutaneous flank meningiomas were treated with verapamil and diltiazem. Serum drug levels of these medications verified that the drugs were reaching concentrations that would be found in patients being treated for hypertension. Growth inhibition was observed with modest results. No long-term "cures" were found. There is evidence that calcium channel antagonists can potentiate the effects of chemotherapeutic drugs. Human glioma tumor growth is inhibited by verapamil alone and more dramatically in combination with the chemotherapeutic agent 1, 3-bis (2-chloroethyl)-1-nitrosourea (BCNU) both *in vitro* and *in vivo*. In fact, the cytotoxicity of many different standard anticancer agents is augmented by calcium channel antagonists in a number of tumor cell types. Currently, tests about calcium channel antagonists coupled with the two chemotherapeutic agents most commonly used for the treatment of meningioma (hydroxyurea and RU486) might comprise a more effective treatment for growth inhibition of meningiomas [179].

6.11.10 Mitogen-Associated Protein Kinase Inhibition:

Platelet-derived growth factor may act as an autocrine/paracrine stimulator of meningioma growth. PDGF-BB has been shown to stimulate DNA synthesis in human meningioma cell lines.75 Johnson et al75 explored the intracellular pathways by which PDGF exerts its mitogenic effects by performing Western blot analysis for mitogen-associated protein kinase (MAPK). MAPKs are a family of serine/threonine kinases implicated in the regulation of cell proliferation and are thought to be a part of the kinase cascade that transduces receptor signals. Activation by growth factor tyrosine kinases phosphorylates and activates MAPK, which enters the cell nucleus to phosphorylate numerous proteins including transcription factors, RNA polymerase II, and cytoskeletal proteins. These investigators performed Western blot analysis on cultured human meningioma cells to show that MAPK and phosphorylated (activated) MAPK were present. The authors found that treatment with PD098059 (a selective inhibitor of MAPK phosphorylation/activation) on proliferating meningioma cells stimulated with 10% fetal bovine serum produced a 52% to 84% loss in [3H]-thymidine incorporation. Also, PD098059-treated meningioma cells showed partial or complete loss of phosphorylated MAPK after 3 days of treatment. The addition of PDGF-BB to meningioma cell cultures resulted in an increase in [3H]-thymidine incorporation and phosphorylation of MAPK. Co-administration of PD098059 completely blocked PDGF-BB's stimulation of [3H] thymidine incorporation and cell proliferation along with reduced MAPK phosphorylation. These findings indicate that MAPK is expressed in meningioma cells and transduces mitogenic signals of PDGF, thereby contributing to the growth of human meningioma [180].

6.11.11 Gene Therapy:

Gene therapy is an emerging technology that offers a therapeutic option for incurable brain tumors. Chauvet et al. (1997, Neurosurgical Focus) have successfully infected a canine meningioma with a recombinant adenovirus vector via selective intra-arterial injection. Specific targets for gene therapies in patients afflicted with meningiomas associated with NF2 is transfection with Merlin, the wild-type NF2 gene. Ikeda et al. showed the feasibility of gene transfer by infecting the wild-type NF2 transgene into human meningioma tumors excised from patients with and without NF2, using a herpes simplex virus. Western blot analysis confirmed that vector-mediated gene transfer mediated the expression of the NF2-

encoded polypeptide Merlin and that overexpression of Merlin significantly inhibited the growth of both NF2-negative and NF2-positive human meningioma cells when compared with controls. Dirven et al. (Journal of Neurosurgery, 2002) proved that the adenovirus viral vector could be altered to target specific tumor receptors on meningiomas. [14, 45, 56-78, 83-99, 104, 106, 109-119, 129-132, 134-149].

6.12 DIRECTIONS FOR FUTURE STUDIES FOR MENINGIOMAS:

Perry et al. and the concerned publications along with Mayo Clinic scheme [9-15, 22-48, 59-68, 118-142] seem to be the most objective WHO classification system to grade meningiomas.

In the future, appropriate categorization can guide therapy and will allow further objective studies to assess therapeutic modalities. Research in epidemiology and etiology has lagged behind that for more malignant intracranial neoplasms. Study of risk factors for meningioma remains challenging. Two main known risk factors: Genetic predisposition and high dose radiation exposures account for a small proportion of cases.

Although a role for hormones is possible, whereas the gender aspect of meningiomas is given and known concerning male : female distribution, little specific or consistent data exist on hormonal risk factors. Epidemiologic tools may be used to collect and define appropriate subject data from well-characterized source populations, being mindful of detection or diagnostic bias in patient ascertainment, in an effort to delineate risk factors both for the overall group of meningioma patients as well as for specific subgroups. High quality follow-up data for sufficient time periods must be collected on meningioma patients to obtain representative estimates of sex- and age-specific rates for recurrence, quality of life and overall survival.

In addition to the collection of data on environmental risk factors such as hormone use, new projects will need to consider the inclusion of information on relevant genetic variants derived from ongoing whole genome and gene pathway scans. In addition to exploring environmental and genetic factors for meningioma risk separately, the interaction between the two must be examined.

For example, the integration of environmental risk factors such as oral contraceptive use or radiation exposure with information on genetic polymorphisms in steroid hormone or DNA repair genes may help researchers to understand the complex relationship between genetic susceptibility and environmental exposures in the development of meningioma. Given the large numbers of subjects needed to study such gene-environment interactions, especially within defined subsets of meningioma such as the rare atypical and malignant subtypes, collaborative, multi-center efforts between a variety of researchers will be needed, including experts from such fields as neurosurgery, epidemiology, genetics, statistics, and neuropathology.

Meningioma epidemiology and etiology will benefit from the increased size and quality of disease reporting to cancer registries (such as the USA by the Benign Brain Tumors Act of 2002 and multicenter studies in Europe). These studies will facilitate a rapid and thorough investigation into the genetic susceptibility factors for meningioma via genome-wide association and whole genome sequencing in the near future. The collection of blood and tumor material must accompany such studies to facilitate the rational classification of the disease into etiologic subtypes to further specify genetic, immunologic, and environmental risk factors. Exposure assessments will continue to hinder progress in meningioma case–control studies, which are hampered by information bias because of poor or differential recall by study subjects, and the lack of verifiable biomarkers of exposure since information is obtained in retrospect.

Large cohort studies in the future may help to ameliorate this problem, and large linked health databases may help study iatrogenic risk factors such as diagnostic and therapeutic ionizing radiation, and therapeutic hormone use.

7. CONCLUSIONS

Most meningiomas are benign (WHO Grade I) tumors; however atypical (WHO Grade II) and anaplastic meningiomas (WHO Grade III) can be found in approximately 6-10% of cases. In addition, metastases are unusual. Available evidences were reported, which had resulted in the current WHO classification.

Among other markers, the most reliability is on the side of EMA, with immunoreactivity in 50–100% of meningiomas. Immunohistochemical staining with the MIB-1 antibody (Ki-67) has consistently correlated with meningioma recurrence.

Other markers correlate with higher-grade meningiomas include the bcl-2 proto-oncogene, p53, p51, alterations in tumor suppressor genes, Fas-APO1 (CD95) transmembrane protein, the extracellular matrix protein Tenascin, and five novel meningioma-expressed antigens. These markers may provide in the future both identification of refractory meningiomas and "novel" therapeutic targets. Many studies indicated that MIB-1 LI and p53 protein expression were good indicators of histological grading in meningioma and may be particularly valuable for distinguishing borderline atypical and anaplastic meningiomas. Brain invasion is a prognostic parameter independent of grade, MIB-1 LI and p53 expression.

Complete surgical resection is the first-line therapy for meningiomas. On the other hand, patients with asymptomatic small benign meningiomas can be followed up without a surgical resection, but in symptomatic patients or if the size of the tumor is increasing significantly, then a possibly complete excision should be performed.

However, tumor location and biological aggressiveness can make a "surgical cure" impossible. The combination with the endovascular treatment, provide a better and safer therapeutic strategy. For recurrent previously resected tumors, re-resection is recommended followed by radiation therapy (RT) in selected cases.

For the majority of incompletely resected or recurrent tumors not previously irradiated, RT is administered. RT may be administered as either conventional external-beam radiation therapy or stereotactically by linear accelerator, IMRT, Gamma Knife, or Cyberknife radiosurgery. Advocates of stereotactic RT and brachytherapy have suggested this management in lieu of surgery particularly in high-risk patients, meningiomas in eloquent or surgically inaccessible locations, and elderly patients.

Chemo- or hormonal therapy may be considered, if other methods have failed. Not with standing limited data, hydroxyurea has been modestly successful in patients with recurrent meningiomas. Antiprogesterone treatment can also be considered in recurrent benign meningiomas. Immunotherapy with Interferon-alpha and chemotherapy should be reserved for all cases of recurrent meningiomas (benign, atypical, and malignant) when all the standard therapies have failed or contraindicated.

Blockade of the growth hormone receptor by Pegvisomant may soon hold a role, as studies showed results accordingly, whereas novel systemic treatment options include angiogenesis inhibition, meningioma cell growth inhibition, growth factor inhibition and blockade of intracellular secondary pathways / calcium channel blockers and gene therapies.

Although no significant function exists for chemotherapy currently, but a role for growth factor (PDGF, VEGF) inhibitors may be established in the future.

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