MetPitNETs DEVELOPMENT AFTER ADENOMA RESECTION AND SUBSEQUENT SRS : a review from literature

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Abstract: MetPItNETs (Metastatic Pituitary Neuroendocrine Tumor) are extremly rare pituitary tumor. MetPitNETs - pituitary carcinoma can present at any age typically presents in the third to fith decade of life in patients with preexisting pituitary adenoma. 207 patients with primary diagnosis of MetPitNETs described in the literature up to 2023, drawn from 128 full texts and 138 in PDF, in the last year full text views 19, PDF 28.

In WHO 2022 clasification adopted the term Pituitary Neuroendocrine Tumor (PitNET). The first group pituitary hormon-secreting cells the clinical behavior of some pituitary tumors „ adenomas“ referred to as very benign tumors. And 2nd group MetPitNET – Metastatic Pituitary Neuroendocrine Tumor – call before carcinoma. Incidency of PitNETs acounting approximately 10-20% of all intracranial neoplasms although the vast majority >90% are benign, a small percetage < 2% are aggressive PitNETs (AgPitNETs), pituitary carcinomas -metastatic PitNETs (MetPitNETs) only 0.2% of case.

Medical history and physical exam: Patient, 61 years old, XII/2007 primary dg.: Pituitary macroadenoma, afunctional, operation I/2008 – subtotal resection. Histology. pituitary adenoma M8272/0, mitotic figures are found quite sporadically. VI/2009 – MRI residue, followed by stereotactic radiosurgery (SRS) of the residue (Leksell gamma knife) IX/2009. Further MRI follow-up 2008-2014 every 1y., 2014-2020 á 2yy., (II and XII/2020) and 2023 and 2025. MRI 2023 – macroadenoma residue in a lighter progression of about 3mm in sagittal projection compared to above 2020. After MRI complete craniospinal 2025 with the finding of multiple spread of tumors in the area of the meninges in the posterior cranial fossa, and the upper cervical spine the surgery with histological di-agnosis was indicated – diff. dg. meningomatosis after irradiation or other pathology. Histology : MetPitNET M8272/3, Ki-67 2%diffusely, mitotic activity 1 mitose/10HPF, Immunophenotype neoplasia: synptophysin +, chromogranin +, SSTR2A + Intensive nuclear accumulation of p53 immunohistochemically demonstrated in a significant number of tumor cells, approximately 2% (p53 wildtype).

Discusion: Therefore, reported latency periods of natural develope MetPitNETs vary from 4 month to 18yr, with a mean interval of 6,6yr..After SRS treatment 5-, 10-, and 15-year risk of malignant transformation was 0.5% (95% CI, 0.0%-0.9%), 0.8% (95% CI, 0.0%-1.8%), and 2.4% (95% CI, 0.0%-5.5%), respectively.The interval from the initial diagnosis of PitNETs to the transformation ranged from 1 to 20 years, with an average of 6.25 } 4.19 years. The transformation often occurred following recurrence of the tumor after surgery. The treatments or events before the transformation were surgery (88.9%), radiotherapy (33.3%) or pituitary apoplexies with clinical symptoms (7.4%), which might promote the transformation of PitNETs as in some malignant tumors.

Conclusion: From the literature, this is probably the first malignant transformation of non-functional adenoma treated in combination surgery and subsequently SRS residues in 1 year. Malignant transformation occurred after 18 years, of which the average natural transformation is 6.6 years and mailing transformation after SRS increases from 5 to 15 years (0.5%, 0.8%, 2.4%).

MetPItNETs are extremly rare pituitary tumor. MetPitNETs - pituitary carcinoma can present at any age typically presents in the third to fith decade of life in patients with preexisting pituitary adenoma. 207 patients with primary diagnosis of MetPit-NETs described in the literature up to 2023, drawn from 128 full texts and 138 in PDF, in the last year full text views 19, PDF 28. (14)

In WHO 2022 clasification adopted the term Pituitary Neuroendocrine Tumor (PitNET). The major reasons of the nomeclature change were: 1. pituitary hormonb-secreting cells a member of neuroendocrine cells their tumors are therefore neuro-endocrenine neoplasms; 2. the clinical beavior of some pituitary tumors are definiti-on beyond those of „ adenomas“ referred to as very benign tumors. And 2nd group MetPitNET – Metastatic Pituitary Neuroendocrine Tumor – call before carcinoma.

Incidency of PitNETs are second most common brain tumor acounting approximate-ly 10-20% of all intracranial neoplasms and the estmated incidency of clinically sig-nificant tumor is 40 per million persons per years. Although the vast majority >90% are benign, a small percetage < 2% are aggressive. These aggressive PitNETs (AgPitNETs) are defined by the presence of radiology invasion, a high rate of cell proliferation, resistence to conventional treatments and /or hight propensity for recurrence. Lastly, there are the rare pituitary carcinoma, also known as metastatic PitNETs (MetPitNETs), which account for only 0.2% of case and are defined by the presence of craniospinal or distant metastasis.

Medical history and physical exam: Patient, 61 years old, December 2007 primary dg.: Pituitary macroadenoma, afunctional, on MRI with haemorhagical apoplexy, al-ready signs of central hypothyroidism and hypocorticism, comp. by substitution ther-apy, left-sided hemianopsia, central hypogonadism, not yet substituted. operation I/2008 – subtotal resection, histology. pituitary adenoma M8272/0, mitotic figures are found quite sporadically. VI/2009 – MRI residue, followed by stereotactic radio-surgery (SRS) of the residue (Leksell gamma knife) IX/2009. Further MRI follow-up 2008-2014 every 1 year, 2014-2020 á 2 years, 2020 – follow-up after a year, followed by 2023 and 2025. MRI 2018 – small residues around the perimeter of the saddle more on the left and parasellar on the left, the deepened sella practically completely fills the sphenoid cavity. MRI 2023 – macroadenoma residue in a lighter progression of about 3mm in sagittal projection compared to above. 2020. After MRI complete craniospinal 2025 with the finding of multiple spread of tumors in the area of the me-ninges in the posterior cranial fossa, and the upper cervical spine the surgery with his-tological diagnosis was indicated – diff. dg. meningiomatosis after irradiation or other pathology. ***Histology :*** MetPitNET M8272/3, Ki-67 2% diffusely, mitotic activity 1 mi-tose/10HPF, Immunophenotype neoplasia: synptophysin +, chromogranin +, SSTR2A + Intensive nuclear accumulation of p53 immunohistochemically demonstrated in a sig-nificant number of tumor cells, approximately 2% (p53 wildtype).

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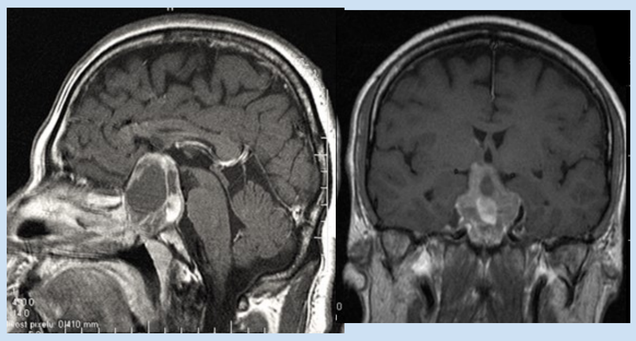

Fig.1 MRI 2007 afunctional adenoma

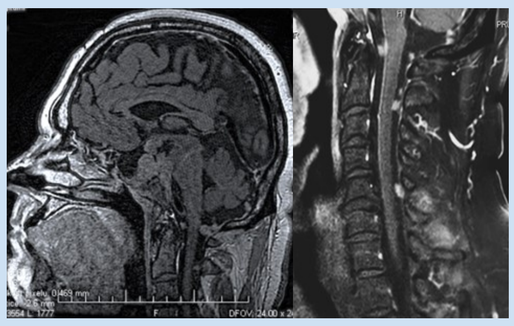

Fig.2 MRI 2025 - MetPitNETs

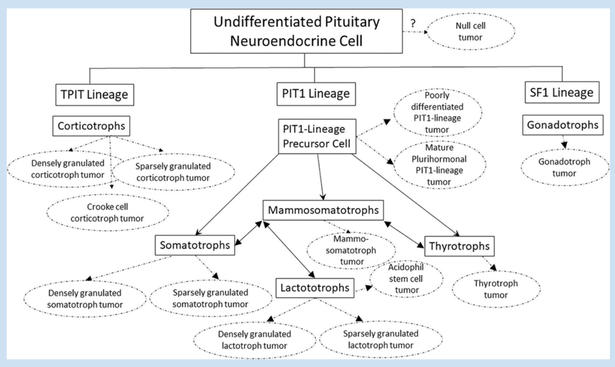

Fig. 3 The Families of Neuroendocrine Cells. (15)

Discussion:

Incidency of PitNETs acounting approximately 10-20% of all intracranial neoplasms although the vast majority >90% are benign, a small percetage < 2% are aggressive PitNETs (AgPitNETs), pituitary carcinomas -metastatic PitNETs (MetPitNETs) only 0.2% of case.

Therefore, reported latency periods of natural develope MetPitNETs vary from 4 month to 18yy, with a mean interval of 6.6yy.(5,11,12,13).

After SRS treatment 5-, 10-, and 15-years risk of malignant transformation was 0.5% (95% CI, 0.0%-0.9%), 0.8% (95% CI, 0.0%-1.8%), and 2.4% (95% CI, 0.0%-5.5%), re-spectively.(6,7,8,9)

The interval from the initial diagnosis of PitNETs to the transformation ranged from 1 to 20 years, with an average of 6.25 + - 4.19 years. The transformation often occurred following recurrence of the tumor after surgery. The treatments or events before the transformation were surgery (88.9%), radiotherapy (33.3%) or pituitary apoplexies with clinical symptoms (7.4%), which might promote the transformation of PitNETs as in some malignant tumors.

Pituitary carcinomas portend a poor prognosis. They are mostly endocrine active tumors with very aggressive clinical features and rapid progression, often unrespon-sive to conventional therapies that are often effective against hormonally active adenomas. Current treatment paradigms include multiple surgical resections, altho-ugh complete resection may be unrealistic given the extent of invasion or with mul-tiple metastatic lesions. Other alternatives, such as radiation therapy, systemic che-motherapy, and medical therapies to treat hormone overproduction are also of limi-ted help (ie, dopamine agonist therapy). Despite aggressive treatments, all of these treatments have proven to be palliative at best. Cytotoxic chemotherapies have yiel-ded disappointing results, despite high proliferative index of pituitary carcinomas. Recurrence with rapid tumor growth is often evident following radiation therapy. Recently, however, some strides have been made with the use of temozolomide, a methylating alkylator agent commonly used to treat malignant gliomas. Here, we re-view the histopathologic features of pituitary carcinomas relative to benign and aty-pical pituitary adenomas, how pituitary carcinomas are best managed in the mo-dern era, and the future directions that will hopefully lead to better treatment for this aggressive malignant disease. (16)

Clinical management of rare pituitary carcinomas is challenging, focusing on a mul-timodal palliative approach (surgery, radiation, hormonal therapy, chemotherapy) to control symptoms and slow progression, with temozolomide showing promise, but long-term survival remains poor, highlighting the need for targeted therapies. Ma-nagement involves maximal surgical resection (often incomplete), targeted medical therapies (like somatostatin analogs or dopamine agonists), radiation, and systemic chemotherapy (e.g., temozolomide), aiming to manage hormone excess and tumor bulk. (9)

Conclusion: From the literature, this is probably the first malignant transformation of non-functional PitNET treated in combination surgery and subsequently SRS residues in 1 year. Malignant transformation occurred after 18 years, of which the average natural transformation is 6.6 years and mailing transformation after SRS increases from 5 to 15 years.

Management Approach

A multidisciplinary team (neurosurgeon, endocrinologist, neuro-oncologist) manages these complex cases, often following an algorithm that incorporates these treatments to prolong survival and improve quality of life.

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