Pituitary Carcinoma: Rare Disease with Difficult Diagnosis and Treatment

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ABSTRACT
Although pituitary tumours are common, pituitary carcinomas are very rare. They are defined as adenohypophyseal tumours with metastatic activity within and outside the boundaries of the central nervous system (CNS). They usually spread to the other parts of the body, by the time they are diagnosed. Because so few cases of pituitary carcinoma have been reported worldwide, it is difficult to learn much about them, and it is difficult to diagnose and treat them. Pituitary carcinomas cannot be distinguished from benign pituitary tumours only on the basis of clinical findings and imaging. Presence of metastases is indicative of carcinoma. Many molecular markers for pathogenesis have been proposed, but none so far is a reliable predictor of disease progression or outcome. Treatment for pituitary carcinomas includes surgery, radiotherapy, and chemotherapy. The paucity of reported cases and literature on pituitary carcinomas renders necessary further research into underlying mechanisms, diagnostic findings, and novel molecular targets for therapy.

Keywords: Pituitary carcinoma, adenohypophyseal tumours, central nervous system, metastases, diagnosis, management.

I. INTRODUCTION
10% to 20% of primary intracranial neoplasms are reported to be from pituitary gland, the bulk of which is formed by benign pituitary adenomas [1]. In contrast to benign pituitary adenomas, pituitary carcinomas are very rare tumours, accounting for only 0.1%-0.2% of all pituitary tumours as malignant transformation is quite rare in pituitary adenomas [2]. Pituitary carcinoma is defined by the presence of a pituitary tumour that is either noncontiguous with the primary sellar tumour and/or a pituitary tumour that has metastasized to sites distant from the pituitary. Due to the rarity of these tumours, no gender or age predilections are evident. The majority of the cases are hormonally active, with clinical findings and biochemical investigations indistinguishable from those of adenomas [3]. Because of being rare, they are difficult to diagnose and treat. The small number of cases has even restricted clinical trials to study pathogenesis, tumorigenesis, diagnosis, and management. Hence, the diagnosis and management are largely driven by few retrospective studies and case series.

II. CASE PRESENTATION
We came across a case of 29 year old female patient, who presented with history of increased urine output, frequent headaches, fever and vertigo for last 2 months. On examination, patient had diplopia and mild drowsiness. Her vitals were normal, Pulse rate – 80/min and BP-120/80mmHg. On clinical examination, there was bilateral
V1 nerve palsy with papilloedema. She underwent various investigations. Her Hb was 11.2 gm/dl, TLC – 5000/cumm with 56% neutrophils. No atypical cells were reported in peripheral blood. Platelet count was 120,000/cumm. Peripheral smear was negative for malaria parasite. Biochemical investigations – Random Blood Sugar was 162mg/dl, unremarkable Liver profile, S. Na+ - 13.5meq/L, S. K+ - 4.24 meq/L. On CSF examination, protein was increased, 104.8mg/dl with total cells 520/cumm and 80% lymphocytes. No atypical cells were reported in CSF. CSF gene expert was negative for mycobacterium and ADA was also normal. Her S. Prolactin was 32.5 ng/dl, TSH – 0.04 uIU/ml, S. FT4 was 7.71 ng/dl, ACTH was 5 pg/ml and GH was 0.13 ng/ml. Urine specific gravity was 1.005. On the basis of investigations done so far, a conclusion of Diabetes Insipidus with ACTH, GH and TSH deficiency was made. MRI brain revealed mass lesion in sella with suprasellar extension. The pituitary stalk was not visualized separately. The lesion showed focal blooming on GRE sequence, heterogenous post contrast enhancement and measured 13×16×23 mm (Fig. 1). There was leptomeningeal enhancement with infarcts in left temporal region and splenium of corpus callosum. MRI findings were suggestive of Pituitary Macroadenoma with apoplexy. Patient was taken up for surgery. Endoscopic transcranial transhenoid excision of the pituitary tumour was done. Tumour was vascular firm. The tumour was resected in multiple pieces and sent for histopathology. The histopathological examination of the tumour tissue bits revealed malignant cells having markedly pleomorphic round to oval nucleus, coarsely granular to clumped chromatin, prominent 1-2 nucleoli and moderate amount of clear to vacuolated cytoplasm. Fair number of atypical mitotic figures, tumour giant cells and necrotic areas were seen (Fig. 2). On Immunohistochemistry (IHC), Ki-67 index was 70-80% and p53 was positive in 60% of tumour cells. ACTH, FSH, GH, and LH were negative on IHC. A diagnosis of mitotically active pituitary tumour – suggestive of pituitary carcinoma was made. The patient had uneventful immediate post-surgical period and recovered well. She was started with radiation therapy after 3 weeks of surgery. After Radiotherapy, the patient improved. Diplopia and headache disappeared. Her PET scan after RT showed complete resolution of the pituitary mass. But the patient again started having headache and visual symptoms after one month of radiotherapy. Repeat MRI showed irregular ill-defined heterogenous enhancement in the sellar and suprasellar regions with enhancing nodular lesions. The distal pons and medulla revealed contrast enhancement – secondary spread from pituitary carcinoma. Post RT changes and chronic ischaemic changes were also seen. Gradually the patient deteriorated and expired 2 weeks later. The patient expired within 5 months of surgery.

III. DISCUSSION

WHO classification of pituitary tumours underwent revision in 2017. The new classification focuses on adenohypophysial cell lineage for the designation of tumours. Hypophysal tumours account for 15% of all intracranial tumours. 35-40% are locally invasive, whereas only 0.1-0.2% are found to develop pituitary carcinoma. Pituitary carcinomas (PCa) are rare malignant neoplasms, composed of adenohypophysal cells with either nervous system or systemic metastases. “Atypical adenoma”, a previous category is now eliminated from the new WHO classification due to poor reproducibility and predictive value. Assessment of tumour mitotic activity, proliferation markers like Ki67 and clinical parameters such as invasion are recommended to predict the aggressiveness of the pituitary tumours [4], [5]. However, still none of these features reliably predict the occurrence of pituitary carcinoma. Most of the pituitary carcinomas reported in literature developed in the setting of a known macroadenoma that exhibited significant suprasellar extension and cavernous sinus invasion [5]. To the best of our knowledge, < 200 cases of PCa have been reported to date.

A. Pathogenesis

Pituitary carcinomas whether occur de novo or progress from atypical/macro adenoma is still unknown. Pituitary tumours can be malignant and may declare their aggressive...
behavior early, from the outset with unresponsiveness to
standard therapy and/or can transform from benign tumour
quickly after surgical debulking or present later in the course
of treatment [6], [7]. However, most PCs are believed to
arise from aggressive pituitary adenomas that convert to
malignant tumour, leading to distant metastases. The
supportive evidence to this comes from [1] usual
presentation as macroadenoma (>1 cm), with multiple
recurrences despite treatment; [2] progressive accumulation
of genetic aberrations. The reported latent periods for benign
adenomas to progress to carcinoma vary widely, from 4
months to 18 years, with a mean interval of 6.6 years [8], [9].

B. Clinical Presentation

Pituitary carcinoma can present at any age but typically
presents in the third to fifth decade of life in patients with no
clear gender predilection [10]. However, prolactin (PRL)
secreting benign tumours from which pituitary carcinomas
generally originate are commoner in males, and it points to
some form of sex steroid hormone independence just as in
breast or prostate tumours [11].

Pituitary carcinomas from an endocrine standpoint, often
behave identically to benign pituitary tumours. As many as
80-88% of all PCs tumours are hormonally active, among
these, prolactin and adrenocorticotropic hormone (ACTH)
production are most commonly elevated, accounting for
almost 50% of all PCs [1]. Growth hormone (GH),
luteinizing hormone, follicle stimulating hormone and
thyroid stimulating hormone have also been described,
though less frequently. Symptomatic patients usually present
with endocrine disturbances and mass effect. No particular
factors can reliably differentiate between the benign
pituitary adenomas and those which show aggressive
behavior and change/transform to carcinoma. The clues to
raise clinical suspicion of aggressive tumour phenotype
include unresponsiveness to treatment and/or escalating
serum PRL level and/or tumour growth despite adequate
dopamine agonist treatment in a compliant patient. It has
been found in the literature that PRL-secreting carcinomas
spread systemically more commonly than ACTH secreting
carcinomas with predilection to liver. In contrast to that, GH
secreting carcinomas present more commonly with
cerebrospinal metastasis [12]-[14].

C. Diagnosis

Pituitary carcinoma is so rare, that it always a diagnosis
of exclusion. In our case also, it was diagnosed as the
tumour showed very high proliferative index and was
unresponsive to the treatment. Laboratory tests usually show
highly elevated hormone levels despite adequate surgical
clearance of the tumour, suggesting the presence of
metastasis [15]. The two main differential diagnosis of
pituitary carcinoma include: 1) Pituitary adenoma; 2)
Metastatic tumour. Metastasis to pituitary is again a rare
phenomenon and accounts for only 1.8% of all metastasis
and 1% of all pituitary cancers. Breast and lung are most
common primaries [16]. Histologically, pituitary carcinomas
may look like typical adenomas but the presence of
increased mitosis; nuclear pleomorphism and tumour tissue
necrosis are often useful indicators of more aggressive
behavior [17].

One must be mindful that histopathology and resultant
behavior may change in the course of disease. A through
microscopic evaluation of the tumour, both from the
primary and metastatic sites remains crucial in confirming
diagnosis and assessing best treatment options. Immunohistochemical profile of the primary as well as
metastatic tumour can be helpful [13].

There is a wide range of molecular markers for an
invasive phenotype, which include Quantitation of
proliferation markers – Ki67, proliferating cell nuclear antigen (PCNA) and tumour suppressor gene - p53 [13],
[18]-[20].

Most pituitary adenomas have low Ki67 labeling index
(1-2%), levels above 3% are unusual and indicative of an
atypical pituitary tumour. Salehi et al reported 11.9+/−3.4%
of mean Ki67 in pituitary carcinomas, as compared to 1.44+/-
0.15% in noninvasive adenomas. A Ki67 value greater than
10% has been proposed by few authors to be an independent
marker of atypical tumours. However, other studies have not
observed such a clear distinction. According to us, Ki67
proliferation index with other atypical features on
histopathology suggest atypical adenomas/carcinomas [18].
Another marker used in pituitary carcinomas is PCNA,
however, it is less reliable marker than Ki67. Scheithauer et
al reported a higher PCNA labeling index in metastatic
pituitary tumours with a median of 72% (range 8-98%) as
compared with adenomas with median of 53% (range 0-
93%) [19].

The tumour suppressor p53 protein is also used in pituitary
carcinomas. Tanizaki et al found that all seven of seven
pituitary carcinoma cases exhibited p53 immunopositivity
compared with 5 to 70 pituitary adenomas (7.1%) [20].

It is important to note that none of these markers’ values
are definite for the diagnosis of pituitary carcinoma. A
holistic approach is required for the correct diagnosis which
includes, atypical cellular morphology, higher mitotic
activity (Ki67/MIB index), and p53 as variables
predisposing to the development of carcinoma along with
radiological and clinical findings. Zemmoura et al identified
angiogenesis, vascular invasion, gene upregulation, and
allelic loss of chromosome 11 as potential factors of
premalignancy in prolactinomas [21]. Metastatic
development has also been associated with increased
activity of Bcl-2 modulated telomerase, topoisomerase-2-α,
COX-2 and galectin-3. Galland et al found the
overexpression of 4 genes common to adenomas and
metastatic activity (IGFBP5, MYOS5A, FLT3 and NFE2L1),
being precursors of tumour cell migration [13], [22].

D. Management

Pituitary carcinomas are generally associated with a poor
prognosis and patients with systemic metastases have a
median survival of 12 months, whereas those with
metastases confined to the central nervous system live
longer with an average of 2.6 years [23]. The treatment of
pituitary carcinomas remains multimodal and includes
surgical resection (transsphenoidal and transcranial), linear
accelerator (LINAC) and proton beam based fractionated
radiotherapy, single dose GKRS, chemotherapy, immunotherapy and the use of other pharmacological agents targeting hormone production itself [13], [24].

First line of therapy involves surgical resection; however, they are rarely curative due to invasive nature or incomplete resection. Surgery relieves compressive symptoms and symptoms due to excessive hormone secretion. However, some argue against surgery hypothesizing that surgical manipulation could potentially contribute to metastatic seeding [5], [25].

Hormone targeted therapy involves agents aiming primarily at controlling biochemical hypersecretion and proliferation to reduce hormone production and slow down tumour proliferation. Higher doses and various drug combinations are used to treat carcinomas [5], [12]. Dopamine agonists (DAs) are given to patients with hyperprolactinemia. Bromocriptine and cabergoline have been used to control adenoma size and secretion with a success rate of 80-95% [26]. Given the expression of estrogen receptor, antiestrogens have been tried in occasional cases, but results have been disappointing. Therapeutic outcomes of short and long acting somatostatin analogues (SSAs) like octreotide, pasireotide, etc. and growth hormone agonists like pegvisomant, have been variable. One case of combination pasireotide-temozolomide therapy in a patient with an ACTH secreting metastasized pituitary carcinoma has been reported [26], [27].

There is no consensus on standardized protocol for chemotherapy. Various combinations have been tried, however, due to rarity of pituitary carcinoma, no randomized control studies of systemic chemotherapy have been conducted. Pituitary carcinomas have high proliferation index and in some way are importantly different from other cancers as they respond poorly to the standard chemotherapy regimens that offer responses in adenocarcinomas or sarcomas. Until recently, the most commonly used cytotoxic drugs were cyclo-hexyl-chloroethylnitrosourea (CCNU) in combination with 5-fluorouracil (SFU) [5], [28]. Temozolomide (TMZ) used for the treatment of glioblastoma multiforme, has shown success in various subtypes of pituitary carcinoma and has quickly become the first-line therapy. Temozolomide is administered orally (100% bioavailability), crosses blood brain barrier, and is not cell cycle specific. TMZ is converted to a methylating alkylator agent, MRTC which induces DNA damage at any point in cell cycle through base pair mismatch. The optimal dose and duration of TMZ in pituitary carcinoma are poorly defined. Most studies have reported short-term treatment periods of between 6 and 9 months, although a few long-term responses of up to 24 months have been described. A dosing regimen between 150 and 200 mg/m² has been employed in most of the studies. In a meta-analysis of 54 patients treated with TMZ, the overall 5 year survival (OS) was 57.4% for atypical adenoma and 56.2% for pituitary carcinoma [7], [29].

Newer studies have theorized on the application of a range of alternative agents including mTOR inhibitors (rapamycin +/- somatostatin analog) and R-roscovitine (CDK2/Cyclin E inhibitor) for ACTH tumours and anti-VEGF antibody treatment and EGF receptor (Erb1 and Erb2) tyrosine kinase inhibitors for dopamine resistant prolactinomas. (30) However, further studies regarding their short and long term efficacy are warranted.

Radiation has been extensively used to treat primary sellar tumour and/or metastatic lesions, however, at present; there is no data to suggest that radiotherapy improves survival in pituitary carcinoma. Limitations of radiation mainly include long term hypopituitarism, radiation necrosis and malignant brain tumours [31]. Balancing the potential benefits and risks, adjuvant radiotherapy should be considered in the setting of a clinically relevant invasive tumour remnant with pathologic markers strongly indicating aggressive behaviour.

IV. CONCLUSION

To conclude, pituitary carcinomas are rare tumours with little knowledge available on tumorigenesis, diagnosis, and management. Overall, there remain many unanswered questions. Because clinical presentation is variable and unpredictable, a high index of suspicion is needed to establish a diagnosis of pituitary carcinoma. The study emphasizes the need for more literature on specific molecular biomarkers and genomic profiling to facilitate diagnosis and standardize treatment. A multimodality approach between endocrinologist, neurosurgeon, oncopathologist, radiologist, radiation oncologist and medical oncologist is recommended.

REFERENCES

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