Pituitary Metastasis- A Rare Condition

Aida Javanbakht, M.D§1, Massimo D’Apuzzo, M.D., Ph.D2, Behnam Badie, M.D3,
Behrouz Salehian, M.D1.

1Department of Diabetes, Endocrinology and Metabolism, Beckman Research Institute of City of
Hope, 1500 East Duarte Road, Duarte, CA 91010, USA.

2Department of Pathology, Beckman Research Institute of City of Hope, 1500 East Duarte Road,
Duarte, CA 91010, USA

3Department of Neurosurgery, Beckman Research Institute of City of Hope, 1500 East Duarte
Road, Duarte, CA 91010, USA

Corresponding author:

§Aida Javanbakht, M.D., Department of Diabetes, Endocrinology and Metabolism, Beckman
Research Institute of City of Hope, 1500 East Duarte Road, Duarte, CA 91010, USA.

aidajavanbakht@gmail.com

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Abstract:

Tumor metastasis to the pituitary gland is a rare, not well-documented and life-threatening condition associated with a shortened life span. A better understanding of its clinical manifestations could lead to earlier diagnosis, appropriate therapy, and potentially improving quality of life. Therefore, we retrospectively studied the charts of patients with pituitary metastases who were treated at the City of Hope National Medical Center (Duarte, CA) from 1984 to 2018. We reviewed and analyzed tumor origin, primary pituitary clinical manifestation, duration between primary tumor diagnosis and pituitary metastasis, type of treatment, and patient survival. A total 11 patients were identified with a mean age of 59.2 years and median survival following the diagnosis of metastasis of 10 months. Breast cancer and lymphoma were the most common primary origins in these cases, and diabetes insipidus and panhypopituitarism were the most common clinical manifestations of their metastasis. We also compared our results with reports in the literature published between 1957 and 2018. A total 289 patients with pituitary metastasis have been reported in the literature. Breast cancer was the most frequent primary origin of the metastasis, and visual symptoms were the most common primary manifestation. The posterior part of the pituitary is more susceptible than the anterior to metastasis. Pituitary metastasis may occur as a consequence of successful primary tumor treatment prolonging the chance of seeding. Future studies are needed to determine the molecular mechanism of metastasis to the pituitary.

Introduction:

Pituitary metastasis (Pit Met) is a rare condition first reported for the by Ludwig Benjamin in 1857 and subsequently by Harvey Cushing in 1913(Chiang MF 1990). Detection of Pit Met is difficult, as they are easily missed in imaging studies and patients are frequently asymptomatic.
Previous studies have reported that only 7% of Pit Mets are symptomatic (Freda PU 1995; Teears RJ 1975). There are reports of involvement of the anterior and posterior part of the pituitary gland (Teears RJ 1975). In contrast to pituitary adenomas, metastatic tumors, when detected, are more likely to be located in the posterior pituitary. This likely accounts for diabetes insipidus (DI) being more common in patients with Pit Met than patients with other pituitary pathology.

The exact reasons underlying the predilection of metastasis for the posterior pituitary is unknown. Reports of Pit Met have largely been found in autopsies series performed for reasons unrelated to the presence of pituitary pathology (Beltrami CA 1970; Delarue J 1964; Fassett DR 2004; Metivier AC 2006; Ntyonga-Pono MP 1999; Pozzessere D 2007). In this report, we present a case series of Pit Met from City of Hope National Medical Center, recorded between 1984 and 2018, as well as a review of the relevant literature from 1957 to present.

**Materials and methods:**

**Data collection:**

Chart review was performed on all of patients diagnosed with pituitary metastasis at City of Hope Hospital from 1984 to 2018. Key words employed in the electronic record search included “pituitary,” “metastasis,” and “brain metastasis.” Pituitary adenomas and other primary pituitary tumors (germinoma, chordoma, meningioma, etc.) were excluded. Information abstracted from patient records included tumor origin, primary pituitary clinical presentation, age, sex, type of treatment, presence of other metastases, and survival. Also, analysis was made of the duration between primary tumor diagnosis and pituitary metastasis. The study was approved by the Beckman Research Institute of City of Hope Ethics Committee and consent was obtained from all patients.
Literature review:

A query of PubMed spanning the years 1957 until 2018 was performed using the key words “pituitary metastasis” and “hypophyseal metastasis” and returned 156 manuscripts, 21 of which involved analysis of animals, leaving 135. Four references included in the analysis were identified from the bibliographies of the articles returned via the PubMed search and, excluding any cases from City of Hope left 139 original publications.

Statistical analysis:

Results were summarized using descriptive statistics (mean, median, and percentages, etc.) by a biostatistician using SPSS 16.0 for Windows.

Results:

Case Series at City of Hope:

We identified a total of 11 patients (6 male) with a mean age of 59.2 years (range: 43–76) excluding one adult patient for whom the age was not recorded. There were no pediatric patients with pituitary metastasis. The most common tumors of origins were breast cancer (2 cases) and lymphoma (2 cases). The most common primary clinical presentations were panhypopituitarism (3 cases) and DI (3 cases). Visual symptoms were also noted in 2 patients. In keeping with the natural history of these lesions, several patients did not have any pituitary-related clinical manifestations. Four patients underwent transsphenoidal surgery (TSS); four patients with Pit Met were discovered by biopsy and three were identified at autopsy. At the time of analysis, five patients had died (mean time from diagnosis of Pit Met 2.7 months). The median survival after diagnosis of Pit Met was 10 months. Ten cases had additional known metastases. All case data are presented in Table 1.

Literature Review:
Takigawa T 2011; Tamer G 2009; Tamura T 2013; Tanaka H 2007; Tanaka T 2015; Taniguchi H 2004; Thewjitcharoen Y 2014; Tomoda Y 2005; Turaka A 2012; Uryu K; Uzal MC 2001; Vianello F 2011; Wang A 2016; Wendel C 2017; Yang L 2013; Yılmaz H 2012). In addition, the frequencies of primary symptoms are reported in Table 2, visual involvement was the most common. The median survival time after diagnosis of Pit Met was 10 months. A total of 179 (61.9%) Pit Met patients underwent surgery, and 175 (60.5%) of them had radiotherapy.

Discussion:

Based on our literature reviewing, breast cancer was the most frequent primary origin of the metastasis, and visual involvement was the most common primary manifestation. The posterior part of the pituitary is more susceptible than the anterior to metastasis. Between 0.14 and 3.6 % of all intracranial metastases are in the pituitary (McCormick PC 1989; Nomizu T 1996). It has been estimated that 1.8 % of all surgically-resected pituitary masses are metastases (Fassett DR 2004). The incidence of Pit Met is independent of gender, and most patients were in sixth decades of life. Although diagnostic methods and treatment options for patients with cancers have improved, at the same time the incidence of Pit Met has increased (Komninos J 2004). Clinical symptoms due to the metastasis manifest in 2.5–18.2% of patients with Pit Met (Komninos J 2004).

Symptoms vary from nonspecific manifestation, such as fatigue and headache, to more specific symptoms of polyuria and polydipsia. The frequent absence or nonspecific nature of Pit Met symptoms makes diagnosis difficult delaying detection of early stage disease. In our study, 60% of cases exhibited pituitary dysfunction with clinical manifestation. The most common clinical manifestations were DI and panhypopituitarism (27.7% each). In primary pituitary adenoma, 1% of patients present with DI, so it has been suggested that patients presenting with
DI undergo evaluation for pituitary metastasis via MRI prior to evaluation for the primary tumor source (Morita A 1998). Based on review of the literature, visual problems are the most common first manifestation of Pit Met (Table 2). The difference between our institutional disease rates versus literature-derived rates might be related to late diagnosis of Pit Met and rapid growth of tumors in patients with end stage cancer.

Patients with breast cancer had Pit Met 9.3 times more frequently than other types of cancers (He W 2015; Park Y 2016). Consistent with this finding, review of the literature showed that breast cancer was the most common source of Pit Met (Figure 1). In the City of Hope series contained herein, breast cancer and lymphoma were equally the most common primary metastasis source. It is hypothesized that elevated hormone levels in the pituitary gland, especially prolactin, may attract metastatic cells (Mansoor Q 2012). Recent studies have found that anti HER-2 treatment can facilitate Pit Met (Kam J 2017; Park Y 2016; Peppa M 2009). In contrast, one of our patients with HER2-positive breast cancer developed Pit Met before receiving anti-HER2 treatment. Future studies are needed to understand the role of the anti-HER2 treatment in the development of Pit Met.

Review of the literature revealed lung cancer to be the second most common source of Pit Met. The lung cancers, being mostly asymptomatic, were discovered in the late stages of disease. In another study, Pit Mets were the first metastatic manifestation of the primary tumor in 34.5% of cases and lung cancers were the source of Pit Mets in 50% (Al-Aridi R 2014). Thyroid cancer is the third most common source of Pit Met. Occasionally, papillary thyroid cancer is diagnosed after finding Pit Mets, while the first symptoms in patients with papillary thyroid cancer may be visual (Stojanović M 2013).
The frequency of renal cell carcinoma is low worldwide (Gopan T 2007; Kramer CK 2010), but it is the fourth most common primary site of Pit Met. This raises the question of possible molecular interactions between renal cell carcinoma and Pit Met including pituitary-originating homing signals or specific characteristics of renal cancers that favor pituitary metastasis. Based on data from the literature, the incidence of Pit Met arising from cancers of the cervix, pancreas, nasal membranes, or germinomas is low. However, the rarity of Pit Met suggests a random nature to these, rather pituitary signals attracting the cancer.

When tumors do metastasize, the posterior part of the pituitary is more susceptible than the anterior. The incidence of metastatic involvement of the anterior pituitary varies from 23.7% to 40% (Komninos J 2004). That most Pit Mets locate to the posterior pituitary may be, in part, due to the fact that this region of the gland is supplied by the systemic circulation, whereas the anterior pituitary receives blood via the hypophyseal portal system (Kramer CK 2010). Another explanation might be the difference in sizes of these areas. The posterior part of the gland is smaller than the anterior, suggesting that the same volume of metastasis in the posterior region will result in symptomology sooner. Also, involvement and massive destruction of supraoptic and paraventricular nuclei in hypothalamus, were the synthesis of neurohypophysis hormones take place, by the extension of an infiltrating tumor, can cause diabetes insipidus. In addition, tumor infiltrating, the site of tracks convergence originating from hypothalamic nuclei, at the base of hypothalamus at the origin pituitary stalk, causes diabetes insipidus (Czernichow P 2000; Fujisawa I 2002; I 2004).

As there is no standardization to the treatment of Pit Mets, a number of approaches have been employed including surgical resection, radiosurgery, radiotherapy, chemotherapy, and hormonotherapy. Surgery is used for confirming the diagnosis and decreasing symptoms.
Hypervascularization of the tumor and invasion of the cavernous sinus and other nearby organs make total resection difficult (Zoli M 2013). All therapies, including radiation therapy, surgical resection, and intrathecal chemotherapy may cause panhypopituitarism. In our literature review, 179 of cases had surgery. Regardless of which therapy is selected, experience at City of Hope suggests caution in the use of high dose steroids prior to biopsy of pituitary masses suspicious for lymphoma. Under these circumstances, steroid use and subsequent tapering of the same may mask the diagnosis of lymphoma, leading to a negative biopsy, causing early recurrence, and potentially negatively impacting vision.

Patient survival after the diagnosis of Pit Met depends on the presence of other metastases and the subtype of the primary malignancy. Resection alone, with or without radiotherapy, does not change survival rates (Novák V 2017). The median survival rate after surgical removal of the pituitary tumor is 6 months (Chen CW 2005; Gilard V 2016). Review of the literature determined the mean survival post- Pit Met diagnosis of was 13.6 months. In our case series in City of Hope hospital, median survival after diagnosis of Pit Met was 10 months. The differences in these data could be secondary to earlier diagnosis and more aggressive treatment of metastasis in the City of Hope group.

The present study has a number of limitations. First, analysis of City of Hope cases was descriptive and retrospective with two cases having incomplete medical records. Second, the size of the clinical cohort was quite small, thus limiting the strength of any conclusions drawn. Third, the data was not balanced by a control cohort. And finally, the study was single center based and could be biased by local unaccounted for factors.

Although the detection and treatment of cancers in general have improved, the incidence of Pit Mets has been increasing. Pit Mets may be the initial presentation of many cancers or may
arise during treatment. Physicians should be cautious when a patient presents with extreme
fatigue, or symptoms suspicious for hypothyroidism or hypoadrenalism. The mechanism of
attracting metastatic cells to the pituitary gland is not clear yet. It may be due to the vascular
distribution of the pituitary gland, characteristics of the primary tumor, or yet to determined
features of the pituitary gland milieu. Determining the molecular characteristics of the tumor
and hosting environments will help to elucidate the pathophysiology of this unusual condition.

Declaration of conflict of interest:

B. Salehian Conflict of Interest: Eisai Inc Consultant, Speaker Bureau.
The other contributing authors declare that they have no conflicts of interest.

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Author contributions:

Study conception and design: Aida Javanbakht, Behrouz Salehian.
Acquisition of data: Aida Javanbakht, Behrouz Salehian, Massimo D’Apuzzo, Behnam Badie.
Analysis and interpretation of data: Aida Javanbakht.
Drafting of manuscript: Aida Javanbakht
Critical revision: Behrouz Salehian.

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References:


76) Arq Bras Endocrinol Metabol 54 498-501.
85) Lim WLD, Chng CL, Lim AY. 2015 Thyroid carcinoma with pituitary metastases: 2 case reports and literature review. Case Rep Endocrinol. 2015 252157.


134) Simmons JD PT, Donnellan KA, Harbarger CF, Pitman KT, Griswold R. 2010 A rare case of a 1.5 mm papillary microcarcinoma of the thyroid presenting with pituitary metastasis. *Am Surg* **76** 336v338.


insipidus and Cushing syndrome due to ectopic adrenocorticotropic hormone secretion].

*Nihon Kogyuki Gakkai Zasshi*. **45** 793-798.


Table 1. Summary of pituitary metastasis cases at City of Hope Hospital from 1984 to 2018.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Origin</th>
<th>Age</th>
<th>Sex</th>
<th>Primary pituitary manifestation</th>
<th>Other metastases</th>
<th>Pit Met DX after primary tumor (years)</th>
<th>TX</th>
<th>Survival after Pit Met (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid organ cancers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Breast (HER2-)</td>
<td>49</td>
<td>F</td>
<td>DI</td>
<td>No</td>
<td>5</td>
<td>TSS</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>Breast (HER2+)</td>
<td>54</td>
<td>F</td>
<td>Panhypopituitarism</td>
<td>Bone</td>
<td>5</td>
<td>Chemo</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>Testicular germ cell tumor</td>
<td>52</td>
<td>M</td>
<td>Panhypothyroidism</td>
<td>Lung</td>
<td>Same time</td>
<td>RT</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>Lung carcinoid</td>
<td>43</td>
<td>M</td>
<td>DI</td>
<td>Liver, bone, temporal-parietal</td>
<td>11</td>
<td>TSS</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Colon adenocarcinoma</td>
<td>61</td>
<td>M</td>
<td>None</td>
<td>Same time</td>
<td>1</td>
<td>TSS</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>Yolk sac</td>
<td>NA</td>
<td>M</td>
<td>NA</td>
<td>Liver</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>Papillary thyroid</td>
<td>65</td>
<td>F</td>
<td>None</td>
<td>Intestinal</td>
<td>Same time</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Hematologic cancers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Hodgkin lymphoma</td>
<td>65</td>
<td>M</td>
<td>None</td>
<td>Papillary, thyroid, lung</td>
<td>Same time</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>Diffuse large B cell lymphoma</td>
<td>72</td>
<td>F</td>
<td>Visual involvement, panhypothyroidism</td>
<td>Hypothalamic</td>
<td>5 months</td>
<td>Chemo</td>
<td>36</td>
</tr>
<tr>
<td>10</td>
<td>Eosinophilic granuloma, dendritic cell tumor</td>
<td>55</td>
<td>M</td>
<td>DI</td>
<td>Bone</td>
<td>Same time</td>
<td>RT</td>
<td>43</td>
</tr>
<tr>
<td>11</td>
<td>Multiple myeloma</td>
<td>76</td>
<td>F</td>
<td>Visual involvement</td>
<td>Thyroid</td>
<td>Same time</td>
<td>TSS and RT</td>
<td>84</td>
</tr>
</tbody>
</table>

Pit Met = pituitary metastasis; DX = diagnosis; TX = treatment; HER2 = human epidermal growth factor receptor 2; F = female; M = male; DI = diabetes insipidus; NA = not available; TSS = transsphenoidal surgery; RT = radiation therapy.
Table 2. Frequencies of primary symptoms of pituitary metastasis reported in the literature from 1957 to 2018.

<table>
<thead>
<tr>
<th>Primary pituitary symptom</th>
<th>Number of cases</th>
<th>Percentage of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual involvement</td>
<td>141</td>
<td>48.8</td>
</tr>
<tr>
<td>Panhypopituitarism</td>
<td>109</td>
<td>37.7</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>111</td>
<td>38.4</td>
</tr>
<tr>
<td>Headache</td>
<td>102</td>
<td>35.3</td>
</tr>
</tbody>
</table>
Fig 1. Frequencies of the pituitary metastasis primary sites reported in the literature from 1957 to 2018.