

RESEARCH

Pituitary metastasis: a rare condition

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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 of 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.

Key Words

- ▶ pituitary metastasis
- ▶ diabetes insipidus
- ▶ panhypopituitarism
- ▶ posterior pituitary

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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 (1). 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 (2, 3). There are reports of involvement of the anterior and posterior part of the pituitary gland (3). 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 (4, 5, 6, 7, 8, 9). 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 the patients diagnosed with pituitary metastasis at City of Hope Hospital from 1984 to 2018. Key words employed in the electronic

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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 two 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

According to our search, a total of 289 pituitary metastases have been reported from 1957 to 2018. The mean age of patients was 56.6 years, and 52.9% were female. The frequencies of primary sites are summarized in [Fig. 1](#) (10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140). 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 (89, 141). It has been estimated that 1.8% of all surgically resected pituitary masses are metastases (6). 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 (142). Clinical symptoms due to the metastasis manifest in 2.5–18.2% of patients with Pit Met (142).

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

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

Subject	Origin	Age	Sex	Primary pituitary manifestation	Other metastases	Pit Met DX after primary tumor (years)	TX	Survival after Pit Met DX (months)	Alive
Solid organ cancers									
1	Breast (HER2-)	49	F	DI	No	5	TSS	8	Yes
2	Breast (HER2+)	54	F	Panhypopituitarism	Bone	5	Chemo	5	Yes
3	Testicular germ cell tumor	52	M	Panhypothyroidism	Lung	Same time	RT	4	No
4	Lung carcinoma	43	M	DI	Liver, bone	11	TSS	10	Yes
5	Colon adenocarcinoma	61	M	None	Temporal-parietal	1	TSS	3	No
6	Yolk sac	NA	M	NA	Liver	NA	NA	NA	No
7	Papillary thyroid	65	F	None	Intestinal	Same time	No	1	No
Hematologic cancers									
8	Hodgkin lymphoma	65	M	None	Papillary, thyroid, lung	Same time	NA	NA	No
9	Diffuse large B cell lymphoma	72	F	Visual involvement, panhypothyroidism	Hypothalamic	5 months	Chemo	36	Yes
10	Eosinophilic granuloma, dendritic cell tumor	55	M	DI	Bone	Same time	RT	432	Yes
11	Multiple myeloma	76	F	Visual involvement	Thyroid	Same time	TSS and RT	84	Yes

DI, diabetes insipidus; DX, diagnosis; F, female; HER2, human epidermal growth factor receptor 2; M, male; NA, not available; Pit Met, pituitary metastasis; RT, radiation therapy; TSS, transsphenoidal surgery, TX, treatment.

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 of the primary tumor source (143). 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 vs 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 (144, 145). Consistent with this finding, review of the literature showed that breast cancer was the most common source of Pit Met (Fig. 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 (85). Recent studies have found that anti-HER-2 treatment can facilitate Pit Met (145, 146, 147). 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% (11). 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 (123).

The frequency of renal cell carcinoma is low worldwide (148, 149), 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.



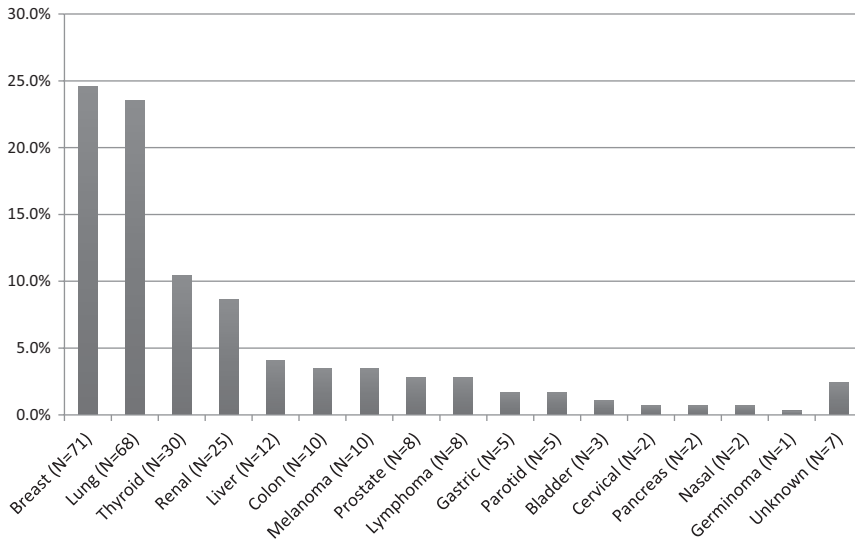


Figure 1 Frequencies of the pituitary metastasis primary sites reported in the literature from 1957 to 2018.

The incidence of metastatic involvement of the anterior pituitary varies from 23.7 to 40% (142). 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 (149). 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 symptomatology sooner. Also, involvement and massive destruction of supraoptic and paraventricular nuclei in hypothalamus, where the synthesis of neurohypophysis hormones take place, by the extension of an infiltrating tumor, can cause DI. In addition, tumor infiltrating, the site of tracks convergence originating from hypothalamic nuclei, at the base of hypothalamus at the origin pituitary stalk, causes DI (150, 151, 152).

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 (153). All therapies, including radiation therapy, surgical resection and intrathecal chemotherapy may cause panhypopituitarism. In our literature review, 179 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 (154). The median survival rate after surgical removal of the pituitary tumor is 6 months (155, 156). Review of the literature determined the mean survival post-Pit Met diagnosis 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 were not balanced by a control cohort. And finally, the study was single center based and could be biased by local unaccounted for factors.

Table 2 Frequencies of primary symptoms of pituitary metastasis reported in the literature from 1957 to 2018.

Primary pituitary symptom	Number of cases	Percentage of cases (%)
Visual involvement	141	48.8
Panhypopituitarism	109	37.7
Diabetes insipidus	111	38.4
Headache	102	35.3



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 be 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 interest

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

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Author contribution statement

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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