Metastases to the pituitary gland

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Only 1% of all pituitary surgeries are performed to treat tumors that have metastasized to the pituitary gland; however, in certain cases of malignant neoplasms pituitary metastases do occur. Breast and lung cancers are the most common diseases that metastasize to the pituitary. Breast cancer metastasizes to the pituitary especially frequently, with reported rates ranging between 6 and 8% of cases.

Most pituitary metastases are asymptomatic, with only 7% reported to be symptomatic. Diabetes insipidus, anterior pituitary dysfunction, visual field defects, headache/pain, and ophthalmoplegia are the most commonly reported symptoms. Diabetes insipidus is especially common in this population, occurring in between 29 and 71% of patients who experience symptoms.

Differentiation of pituitary metastasis from other pituitary tumors based on neuroimaging alone can be difficult, although certain features, such as thickening of the pituitary stalk, invasion of the cavernous sinus, and sclerosis of the surrounding sella turcica, can indicate metastasis to the pituitary gland. Overall, neurohypophyseal involvement seems to be most prevalent, but breast metastases appear to have an affinity for the adenohypophysis. Differentiating metastasis to the pituitary gland from bone metastasis to the skull base, which invades the sella turcica, can also be difficult. In metastasis to the pituitary gland, surrounding sclerosis in the sella turcica is usually minimal compared with metastasis to the skull base.

Treatment for these tumors is often multimodal and includes surgery, radiation therapy, and chemotherapy. Tumor invasiveness can make resection difficult. Although surgical series have not shown any significant survival benefits given by tumor resection, the patient's quality of life may be improved. Survival among these patients is poor with mean survival rates reported to range between 6 and 22 months.

KEY WORDS • pituitary • metastases • diabetes insipidus

Metastatic disease in the pituitary gland accounts for only 1% of all pituitary tumor resections, but appears to occur more frequently with certain types of cancer.^{7,21} Because of its relative rarity, there are comparatively few reports offering discussions of diagnosis and treatment modalities. In this paper, we review the literature on pituitary metastases and summarize the prevalence of this disease. We discuss associated clinical and neuroimaging findings, evaluate recommendations for treatment, and review patient outcomes.

PREVALENCE OF PITUITARY METASTASES

Authors of reports on large autopsy series have stated that pituitary metastases occur in between 1 and 3.6% of patients with malignant tumors.^{1,15,19} If one considers autopsy series in which both the pituitary and surrounding sella turcica have been evaluated, however, rates of metastasis as high as 27% have been reported to occur in this area.²⁴ Breast cancer is the most common tumor to metastasize to the pituitary gland; its frequency is followed by that of lung cancer. Prostate,^{6,17} renal cell,^{14,26} and gastrointestinal cancers,¹¹ and lymphoma,¹⁶ leukemia, thyroid carcinoma,^{2,5} and plasmocytoma^{3,10} have also been reported

(Table 1).⁷ Despite the association with breast cancer, there does not appear to be any significant sex predominance with pituitary metastases.^{15,22,25}

Breast and lung cancer are the two most common forms of malignant tumors, which partially accounts for the high proportion of pituitary metastases from these two types of cancer. In specifically looking at breast cancer, there appears to be an increased rate of pituitary metastases with this malignant tumor. Histological examinations of pituitary glands obtained during hypophysectomy for palliation in end-stage breast cancer and from autopsy series have documented pituitary metastases in 6 to 29% of breast cancer patients.^{1,8,9,18,24} Some authors theorize that the hormonal environment of the pituitary gland may attract breast cancer cells and provide an optimal environment for these malignant cells to thrive, accounting for the higher prevalence of pituitary metastases associated with this disease.

LOCATION OF METASTASES WITHIN THE PITUITARY

Authors of early series have reported that the majority of pituitary metastases occur in the posterior pituitary, but some dispute this claim. In a series of 88 cases of carcinoma that had metastasized to the pituitary, Teears and Sliverman²⁵ reported that 57% of the lesions localized to

Abbreviations used in this paper: DI = diabetes insipidus; MR = magnetic resonance.

TABLE 1

Primary malignant tumors associated with pituitary metastases: a comparison of two studies

Type of Primary Tumor	Percentage of Patients	
	Teears & Silverman, 1975 (88 patients)	Morita, et al., 1998 (36 patients)
breast	40	33
lung	33	36
prostate	3	3
colon/intestinal	2	3
liver	0	3
renal cell	0	3
other	22	19

the posterior pituitary alone, 13% to the anterior pituitary alone, 12% to both lobes, and the remaining to the capsule or stalk. These authors hypothesized that the posterior pituitary, by receiving a direct arterial blood supply, is more likely to develop metastases than the adenohypophysis, which receives its blood supply from the hypophyseal portal system.

Some authors have suggested that certain malignant diseases such as breast cancer may have an increased affinity for the adenohypophysis because of a nascent hormonal attraction. Two series limited to pituitary metastases from breast carcinoma have shown a preponderance of anterior pituitary involvement, with 70 and 82% rates of anterior pituitary involvement, respectively.^{8,18} The reported metastatic involvement of the neurohypophysis and adenohypophysis is summarized in Table 2; there is a trend toward increased rates of anterior pituitary involvement associated with breast cancer.

FINDINGS

Clinical Findings

Based on findings in early autopsy series, it appears that the majority of pituitary metastases are clinically silent. In the autopsy study conducted by Teears and Silverman²⁵ only 7% of pituitary metastases were symptomatic. Among the more commonly reported symptoms are DI, ophthalmoplegia, headache/pain, visual field defects, and anterior pituitary dysfunction (Table 3).

Authors of many studies have reported especially high

TABLE 2

Location of metastases within the pituitary gland

Location	Percentage of Patients		
	Gurling, et al., 1957* (11 patients)	Teears & Silverman, 1975 (88 patients)	Marin, et al., 1992* (36 patients)
anterior pituitary alone	82	13.6	41.6
posterior pituitary alone	18	56.8	16.7
both anterior & posterior pituitary	0	12.5	30.6
capsule, stalk, other	0	17.1	11.1

* Includes breast cancer only.

TABLE 3

Presenting symptoms and signs in patients with symptomatic pituitary metastases

Symptom/Sign	Percentage of Patients		
	Max, et al., 1981 (28 patients)	Branch & Laws, 1987 (14 patients)	Morita, et al., 1998 (36 patients)
DI	71	29	61
anterior hypopituitarism	7	43	47
retroorbital pain/headache	0	69	39
visual deficits	7	50	33
ophthalmoplegia	15	43	25

rates of DI in their series of patients; this condition was thought to be caused by an increased prevalence of posterior pituitary involvement.²⁵ Morita, et al.,²² have noted that DI is more common in patients with symptomatic pituitary metastases than in those with symptomatic adenomas. Approximately 60% of the patients treated by these authors for pituitary metastases had DI, whereas only 1% of their patients with adenoma presented with this condition. Other authors have reported that between 14 and 20% of patients presenting with DI will have pituitary metastases.^{9,12}

Because of the invasiveness of tumors that metastasize to the pituitary, they are also likely to produce visual deficits from suprasellar extension and painful ophthalmoplegia from invasion of the cavernous sinus.^{11,22,23} Many authors emphasize that anterior pituitary hormonal dysfunction is probably underreported in patients with this disease because a significant percentage of patients are likely to decline as a result of their systemic disease, thus masking the symptoms of anterior pituitary dysfunction.

In some patients, symptoms related to pituitary metastases may be the first manifestation of a malignant neoplasm. Morita and colleagues²² and Branch and Laws³ have noted that, in a significant percentage (56 and 64%, respectively) of patients exhibiting symptoms, the pituitary symptoms were the initial presentation of malignant disease.

Neuroimaging Findings

Sensitive and specific criteria for differentiating pituitary metastases from pituitary adenomas have not been reported. Many authors place more emphasis on clinical history than on neuroimaging findings. In older patients, patients with a history of a malignant neoplasm, and patients with symptoms such as DI and ophthalmoplegia, metastasis should be strongly considered for a pituitary mass (Fig. 1). A few imaging characteristics have been reported to be helpful in differentiating pituitary metastases from pituitary adenomas; these include the following: 1) thickening of the pituitary stalk;^{20,22} 2) loss of a high-intensity signal from the posterior pituitary;⁴ 3) isointensity on both T₁- and T₂-weighted MR images;²⁰ 4) invasion of the cavernous sinus;²⁰ and 5) sclerotic changes around the sella turcica.¹³ Although these findings may indicate the possibility of metastases, they are in no way specific for pituitary metastases.

Fig. 1. Gadolinium-enhanced T₁-weighted MR images obtained in a 75-year-old man with a history of renal cell carcinoma who presented with diplopia, due to sixth cranial nerve palsy, and a pituitary mass. *Left:* Axial image revealing a 1.5-cm-wide intrasellar mass. *Right:* Sagittal image demonstrating a pituitary mass with thickening of the pituitary stalk.

TREATMENT FOR PITUITARY METASTASES

Multiple treatment modalities exist for pituitary metastases including resection, radiation therapy, and chemotherapy.¹⁷ Because of the rarity of this tumor and its association with end-stage metastatic disease, no significant studies are available in which these various treatment modalities are compared.

Resection has most commonly been performed via a transsphenoidal surgical approach, but subfrontal and other approaches have been reported. Gross-total resection is difficult for a number of reasons, including the vascularity of the tumor, resulting in heavy bleeding; local invasiveness into the surrounding bone and cavernous sinus; and infiltration of the hypothalamus and optic nerves.^{7,10,17} Reports on two surgical series have indicated no difference in survival attributed to resection. In a review of 36 patients with symptoms, Morita, et al.,²² found no statistically significant difference in survival in the 21 patients who underwent surgery. The authors did note an improvement in survival times when local tumor control was achieved, but this usually required multiple treatment modalities. They also found an improvement in symptoms (visual acuity, pain, and ophthalmoplegia) and quality of life after aggressive tumor resection and radiation therapy. Other authors have confirmed improved quality of life, but no survival benefits associated with surgery.³ Of the presenting symptoms, anterior pituitary hormonal dysfunction appears to be the least likely to improve in response to aggressive management.

In most series adjuvant radiation therapy has been used for pituitary metastases, but there is debate about whether the radiation should be directed to the parasellar region alone or to the entire brain. Proponents of limited parasellar region irradiation favor a limited field to reduce the side effects of whole-brain irradiation. Those favoring whole-brain irradiation have noted that these tumors can spread via meningeal pathways or by direct extension out of the limited treatment field. At this time, there are in-

sufficient data to support one radiotherapy philosophy over the other. Although not reported in the literature, radiosurgery may have a role in the treatment of pituitary metastases.¹⁰

Chemotherapeutic agents have been widely used, but success rates have not been published in the literature on pituitary metastases. As chemotherapeutic advancements continue for the treatment of these malignancies, we may see improvements in outcome.

OUTCOME OF PATIENTS

The vast majority of cases of pituitary metastasis occur in association with multiple systemic metastases and are typically associated with end-stage disease. In an autopsy series, Kovacs¹⁵ found metastatic lesions in other organs in all 18 patients with pituitary metastases. Even in patients in whom no other metastatic disease was noted on the initial metastatic workup report, the prognosis remains grim, because a majority of these patients will harbor microscopic metastatic lesions not detected on evaluation. Morita, et al.,²² reported that 13 of 17 patients without additional sites of metastases at the time of initial diagnosis died of other metastases within 18 months. Mean survival rates have been reported to be between 6 and 22 months, independent of the treatment strategy.^{3,22}

CONCLUSIONS

Pituitary metastases are rarely seen by neurosurgeons but should be considered in the differential diagnosis for older patients, patients with a history of malignancy, and patients with symptoms such as DI or ophthalmoplegia. Although the prognosis is poor because of uncontrolled systemic disease, there may be a role for resection in a select group of patients to alleviate symptoms and improve quality of life.

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