



Review article

Neuro-ophthalmological findings of pituitary metastasis: Case series from a single center and review of the literature

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ABSTRACT

When pituitary metastasis (PM) invades the pituitary gland, it leads to impaired endocrine function and compression and infiltration of surrounding tissues, causing a series of clinical alterations. We presented seven patients with PM evaluated at neuro-ophthalmologic clinic and reviewed neuro-ophthalmological findings of 44 cases with PM in the English literature from 1979 to December 2022. The mean age at diagnosis was 58.1 years, and 45.1% were male. The mean latency period from primary cancer to the diagnosis of PM was 57.6 months. PM is the only presenting sign of malignancy in 11.8% of patients. The mean time from the visual disturbance to the diagnosis of PM was 96.3 days. Visual acuity decreased in 72.5% and 60.8% of cases with visual field defects. 74.2% exhibited a pattern of temporal field defect respecting the vertical meridian. Isolated ophthalmoplegia was found in 37.3% of patients. The most common ocular motor nerve palsy was unilateral III nerve palsy. Breast cancer was the most common primary malignancy. 84.6% entirely or partially relieved the neuro-ophthalmic symptoms after treatment. 51% of patients were alive during a mean follow-up period of 11 months. The mean survival duration was within six months in 65% of deceased patients. For elderly patients with a pituitary tumor, PM should be on the list of differential diagnoses for those with visual impairment, especially ocular motor nerve palsy, even if diabetic insipidus is not present, with or even without a history of malignancy, regardless of the primary tumor site.

1. Introduction

Pituitary metastasis (PM) is a rare cranial tumor with an incidence of 0.87% in all intracranial metastasis [1]. In 1857, Benjamin first reported PM in the autopsy of a patient with melanoma in German, while Harvey Cushing reported the first case in English literature in 1913 [2]. In recent years, the incidence has been gradually higher with the improvement of medical technology and the prolonged survival of the patients [3]. Due to its insidious onset, rapid progression, increased mortality, and poor prognosis, once diagnosed, it is often accompanied by extensive metastasis [4]. Furthermore, it can be the first manifestation of occult cancer or the only site of metastasis. It is challenging to distinguish PM from other sellar masses based on the patient's clinical presentations and radiological features. The diagnosis ultimately needs to be confirmed with the histopathological results [5]. PM is clinically manifested as headache, diabetes insipidus (DI), vision impairment, and adenohypophyseal dysfunction [6]. Sometimes, the rapid progression of PM can severely affect vision in a shorter period. These patients may be first referred to ophthalmologist or neuro-ophthalmologist, and

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Table 1

The clinical characteristics and neuro-ophthalmological findings of pituitary metastasis in our case series.

No.	Age/ Sex	Primary cancer	Pathological diagnosis	Known metastatic sites	Latency between primary cancer and PM (months)	Presenting NO symptoms	Duration of NO symptoms (months)	Ocular examinations			Survival (months)
								Visual acuity (R/L)	Visual field (R/L)	Ophthalmoplegia	
1	57/ M	Lung	Adenocarcinoma	Mediastinum	0.25	Headache, decreased vision	2	20/30, 20/40	Supratemporal quadrantanopia/ Supratemporal quadrantanopia	None	25
2	36/F	Breast	Invasive ductal carcinoma	None	60	Headache, vomiting, and vision loss	10	20/100, FC	Inferonasal and temporal defect/Central scotoma	None	13 ^a
3	54/ M	Prostate	Adenocarcinoma	Sacrum, iliac bone	36	Headache, orbital pain	6	20/30, 20/30	Peripheral constriction/ Unspecific pattern	None	27
4	51/F	Lung	Adenocarcinoma	Mediastinum, adrenal gland, bone	18	Headache and vision loss	3	NA	Temporal hemianopia/ Central scotoma	None	4 ^a
5	74/ M	Esophagus	Adenocarcinoma	Lung	156	Headache and dizziness	0.17	20/40, 20/30	Supratemporal quadrantanopia/ Temporal and inferonasal defect	None	25
6	54/F	Breast	Invasive ductal carcinoma	None	96	Vision loss	12	NLP, 20/ 100	NA/Central scotoma	None	3 ^a
7	55/ M	Kidney	Clear cell carcinoma	Lung	120	Ptosis and diplopia	0.5	20/20, 20/20	NA	Left III palsy with pupillary involvement	2 ^a

F, female; FC, finger counting; L, left; M, male; NA, not available; NLP, no light perception; NO, neuro-ophthalmological; R, right.

^a The patients died during follow-up.

the lack of systemic symptoms such as DI makes the diagnosis difficult, so understanding their neuro-ophthalmologic manifestations and quickly recognizing the nature of PM is essential. Previous studies have been mostly case reports and large studies are lacking. Therefore, an overview of neuro-ophthalmologic manifestations of PM is necessary.

We retrospectively reviewed the clinical data of patients with PMs evaluated by the neuro-ophthalmologist in our center, together with a literature review, to summarize neuro-ophthalmological findings of PM.

2. Methods

A retrospective case series of patients with sellar region tumors were evaluated at the neuro-ophthalmology clinic from February 1, 2020, to August 1, 2022, at the Department of Ophthalmology, Renji Hospital, Shanghai Jiao Tong University, School of Medicine. From 292 patients with sellar region tumors, we identified seven patients (2.4%) diagnosed with PM. Further investigation was performed to evaluate clinical data on patient demographics, symptoms, and ophthalmic, radiological, and histological findings. This study was approved by the Renji Hospital, Shanghai Jiao Tong University, School of Medicine Research Ethics Board and follows the tenets of the Declaration of Helsinki.

We conducted a PubMed search with the keywords “pituitary metastasis”, and 285 literatures were found after literature screening from 1979 to December 2022. The inclusion criteria were: 1. English literature; 2. The cases presenting with neuro-ophthalmological symptoms; 3. The cases with definite pathological diagnosis of PM. The exclusion criteria were: 1. Unidentified primary cancer in the report; 2. To focus on visual symptoms, we excluded the cases presenting with DI; 3. The cases without detailed neuro-ophthalmological examinations. Forty-four cases from 38 papers reported the presenting neuro-ophthalmological symptoms, such as visual field defects, vision loss, diplopia, and ophthalmoplegia, were selected [1,2,7–42]. The patient information, including age, sex, the time elapsed from primary cancer to the diagnosis of PM, sites of metastasis, treatment, and survival time after diagnosis of PM, were collected ([Supplementary material](#)).

3. Results

3.1. Case series

The clinical characteristics and neuro-ophthalmological findings of PMs are listed in [Table 1](#). Best-corrected visual acuity, visual field, and ocular examinations were performed preoperatively. These cases were later confirmed by radiology or pathology, including four males and three females, and median affected ages of 54 years (range: 36–74 years). The primary tumors included two lung cancers, two breast cancers, one renal cancer, one prostate cancer, and one esophageal cancer. The median latency period from primary malignancy to the identification of PMs was 60 months (range: 0.25–120 months), and the median time of symptoms was three months (range: 0.17–10 months). There was no family history of genetic disease or cancer. Three of seven patients had a headache, one of whom was accompanied by nausea, vomiting, and fever (Case 2). Visual acuity was reduced in three cases, and six patients had visual field defects except for one patient (Case 7) who could not perform visual field testing. Ophthalmoplegia from the oculomotor nerve palsy was found in one patient (Case 7).

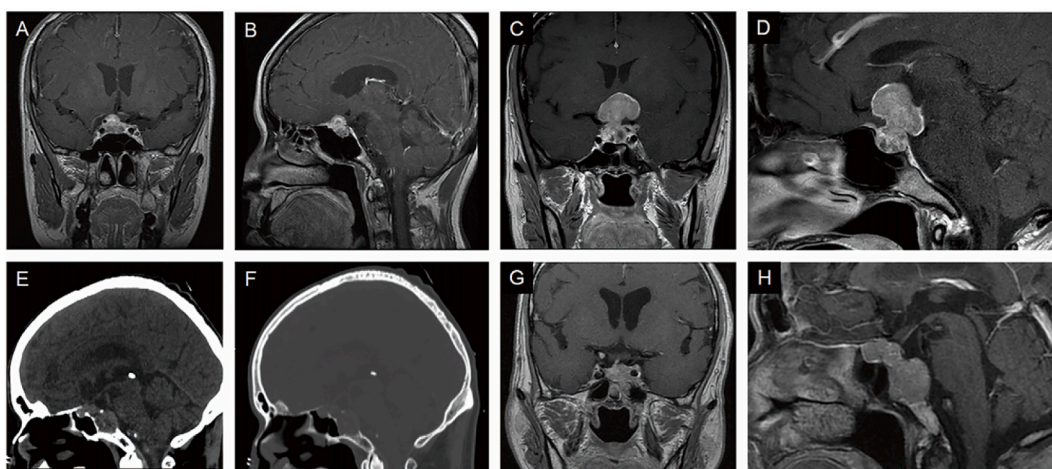


Fig. 1. Neuroimaging of pituitary metastasis. Enhanced coronal (A) and sagittal (B) T1 MRI scans of Case 6 reveal abnormal enhanced nodules at the pituitary gland with adjacent parasellar enhancing dura mater. The optic chiasm is compressed upward without apparent sellar base depression. There is no obvious bone destruction. Enhanced coronal (C) and sagittal (D) T1 MRI scan of Case 2 show heterogeneously enhancing intrasellar mass with suprasellar extension in a dumbbell configuration, causing optic chiasmatic compression. Sagittal head CT scans on the soft-tissue window (E) and bone window (F) demonstrate bone destruction of the sellar dorsum and clivus. Enhanced coronal (G) and sagittal (H) T1 MRI scans of Case 7 show a heterogeneously enhanced intrasellar mass involving the left cavernous sinus and clivus. The pituitary stalk deviates to the right.

Pretreatment endocrine tests were performed in all patients. None of our patients had DI. One patient (Case 2) had anterior pituitary hypofunction, and most of the remainder showed increased prolactin. Six patients were confirmed by pathological diagnosis and one by history and radiology. Each patient underwent pituitary-enhanced CT and MRI preoperatively. MR scans showed T1 hypointense and T2 hyperintense with the (mostly heterogeneous) enhancement of the intra- and supra-sellar mass in 6 cases (Fig. 1A, B, C and D) and expansion to the cavernous sinus in 4 cases (Fig. 1G and H). Measured on MRI, the tumor volumes varied between 0.81 and 15.34 cm³. The optic chiasm and pituitary stalk were found to be compressed in all patients (Fig. 1A, B, C and D). Three patients had a dumbbell-shaped tumor pushing the optic chiasm upward (Fig. 1C and D). On CT scans, five patients had enlarged sella turcica, and one had destruction of the sellar dorsum. The clivus was eroded in 2 patients (Fig. 1E and F). These are listed in Table 2.

During follow-up, the median postoperative survival time was six months (2–27 months). All patients had systemic metastasis found by PET-CT, and Case 3 showed no response to chemotherapy. Six patients had surgery decompression to relieve the visual symptoms. One patient was not sensitive to chemotherapy, and surgery was performed to confirm the pathology. The Ki-67 index was variably elevated in postoperative pathology. Table 1 details the patients' outcomes. Three patients had systemic metastases or cachexia within six months after surgery. Local control of the tumor was achieved in 3 patients, and they were still alive during a 2-year follow-up. Complications after transsphenoidal surgery included one cerebrospinal fluid leak, one transient diabetes insipidus, and three endocrine deteriorations. The causes of death included hydrocephalus in Case 2, metastatic carcinoma in Cases 4 and 6, and endocrine deterioration in Case 7.

3.2. Literature review

We compared seven unpublished cases with 44 cases from the literature, and we analyzed and listed the clinical characteristics of 51 patients with PM in Table 3. The mean age at diagnosis was 58.1 ± 1.7 years (range: 22–76, median age 60). Among them, 23 (45.1%) were male, and 28 (54.9%) were female. Among those with a history of primary cancer (23 in the literature and 7 in our series), the mean latency period from primary cancer to the diagnosis of PM was 57.6 months. In 11.8% of patients, PM is the only presenting sign of malignancy. PM and other metastases were found in 29.4% of patients before the diagnosis of primary malignancy. The mean time from the visual disturbance to the diagnosis of PM was 96.3 days (median: 60 days). 37.3% were diagnosed with pituitary adenoma. Visual acuity decreased in 72.5% and 60.8% of cases with documented visual field defects. 74.2% exhibited a pattern of temporal field defect respecting the vertical meridian. Isolated ocular motor nerve palsy was found in 29.4% of patients. The most common ocular motor nerve palsy was unilateral III nerve palsy, followed by unilateral III and VI nerve palsies and unilateral III, IV, and VI nerve palsies. No case described aberrant regeneration. Four patients had both visual field deficits and ocular motor nerve palsies. Tracing primary cancer revealed that 24% had breast cancer, followed by 16% had lung cancer, 14% had thyroid cancer, and the others originated from the liver, kidney, neuroendocrine tumor, melanoma, prostate, colon, myeloma, choriocarcinoma, and esophagus. Many modalities, such as tumor resection in 58.8% of patients and surgery combined with radiotherapy in 25.5% of patients, were documented for treatment. 84.6% can entirely or partially relieve the neuro-ophthalmic symptoms and rescue the patient's visual function. For survival status, 51% of patients survived during an average follow-up period of 11 months. The average postoperative survival time of 20 deceased patients was 6.7 months (median: 5.5 months), of which 65% died within six months.

4. Discussion

PM may have an insidious onset and is asymptomatic early, with clinical symptoms reported in only 7%–20% of patients [43,44]. With a predilection for the posterior pituitary, it can present with endocrine dysfunction and variable visual symptoms [43]. When the tumor grows rapidly, it leads to invasion or compression of parasellar structures. In contrast to the earlier studies that DI was the most frequent presenting symptom in PM [13], Lithgow et al. reported that visual dysfunction was the most common presentation of PMs [45]. A systematic review found that the incidence of anterior hypopituitarism and cranial nerve palsy is higher than that reported with the advances in neuroimaging techniques [1]. Our study also demonstrated that visual loss was not uncommon, which can be the first

Table 2
The endocrinologic and neuroimaging findings of pituitary metastasis in our case series.

No.	Endocrine examinations	Neuroimaging features	Tumor size on MRI			
			Volume (cm ³)	Length (cm)	Height (cm)	Width (cm)
1	PRL↑	Heterogeneous enhanced on MRI, chiasmal compression	5.17	2.15	2.63	1.76
2	FSH, TSH, LH, ACTH↓	Heterogeneous enhanced, dumbbell-shaped tumor, meninges, clivus and left cavernous sinus involvement, third ventricle and chiasmal compression	11.33	2.72	3.22	2.48
3	LH, FSH, PRL↑	Homogeneous enhanced, clivus and cavernous sinus involvement, and chiasmal compression	0.81	1.13	1.20	1.15
4	PRL↑	Dumbbell-shaped tumor and chiasmal compression	8.71	2.27	2.32	2.23
5	PRL↑	Heterogeneous enhanced, dumbbell-shaped tumor, chiasmal compression	15.34	2.78	3.66	2.90
6	PRL↓	Heterogeneous enhanced with pachymeningeal involvement	2.67	2.09	1.75	1.40
7	Normal	Heterogeneous enhanced, left cavernous sinus involvement	4.19	1.75	1.85	2.49

ACTH, adrenocorticotropic hormone; FSH, Follicle stimulating hormone; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid-stimulating hormone.

Table 3

The clinical characteristics and neuro-ophthalmological findings for 51 cases of pituitary metastasis in unpublished case series and literature review.

	Literature review (n = 44)	Our case series (n = 7)	Overall (n = 51)
Male/Female	19 (43.2%)/25 (56.8%)	4 (57.1%) /3 (42.9%)	23 (45.1%) /28 (54.9%)
Mean age/median age (years)	58.7 ± 1.8/61	54.4 ± 4.2/54	58.1 ± 1.7/60
Mean/median latency period between the diagnosis of primary cancer and PM (months)	54.0 ± 10.7/36 (n = 23)	69.5 ± 21.4/60	57.6 ± 9.5/36 (n = 30)
Mean/median interval between NO symptoms and identification of PM (days)	86.4 ± 15.5/60 (n = 34)	144.3 ± 53.1/90	96.3 ± 15.7/60 (n = 41)
Patients with other metastases prior to diagnosis of PM	28	5	33
Neuro-ophthalmologic manifestations			
Decreased visual acuity	34 (n = 39)	3	37 (n = 42)
Visual field defect	25 (n = 29)	6	31 (n = 35)
Ocular motor nerve palsy	18	1	19
Unilateral III nerve palsy	9	1	10
Unilateral III and VI nerve palsies	5	0	5
Unilateral III, IV and VI nerve palsies	2	0	2
Bilateral IV nerve palsy	1	0	1
Bilateral VI nerve palsy	1	0	1
Primary cancer			
Breast	10	2	12
Lung	6	2	8
Thyroid	7	0	7
Liver	6	0	6
Kidney	4	1	5
Neuroendocrine	3	0	3
Melanoma	3	0	3
Prostate	1	1	2
Colon	2	0	2
Myeloma	1	0	1
Choriocarcinoma	1	0	1
Esophagus	0	1	1
Treatment			
Surgery	24	6	30
Surgery + Radiation	15	0	15
Surgery + Chemotherapy	1	1	2
Surgery + radiation + Chemotherapy	2	0	2
Radiation	1	0	1
Chemotherapy	1	0	1
Radiation + Chemotherapy	1	0	1
Prognosis of NO symptoms	(n = 32)		(n = 39)
Complete response	6	0	6
Partial response	21	6	27
Stable or progressive	5	1	6
Mean/median follow-up period (months)	10.4 ± 1.3/9 (n = 35)	14.1 ± 4.3/13	11.0 ± 1.3/9
Survival analysis (Alive/dead/unknown)	44 (23/16/5)	7(3/4/0)	51(26/20/5)
Mean/median survival duration of demise (months)	6.9 ± 1.1/6	5.5 ± 2.5/3.5	6.7 ± 1.0/5.5
0–6	10	3	13
7–12	5	0	5
13–18	1	1	2

manifestation of PM without any evidence of DI and seriously affects the quality of life of patients. We emphasize that symptomatic PM was the presenting manifestation of primary malignancy in 41.2 % of patients and the only presenting sign in 11.8 %.

Although DI and cranial nerve palsies occur more frequently with PM than other pituitary region masses, the clinical presentation and imaging are insufficient to diagnose. However, on neuroimaging, some features help distinguish PM from pituitary adenoma (PA), including relatively normal size fossa, bony destruction, dural thickening, dumbbell shape, and irregular edges. The enhancement patterns tend to be avid and may also be heterogeneous [46], which aligns with our patients. Therefore, when an elderly patient with a history of cancer has a pituitary mass, PM needs to be suspected when pituitary imaging has these characteristics.

Aaberg et al. found 42% of patients with PM developed ocular motor nerve palsy compared with less than 5% of patients with pituitary adenomas [47]. Castle-Kirsbaum et al. concluded that the development of DI or ophthalmoplegia from any pituitary lesion, even in patients without a known primary lesion, was suggestive of metastasis [6]. Kars et al. suggested that ocular motor nerve palsy strongly suggests nerve compression or infiltration secondary to the invasive behavior of the tumor [48]. The pattern of ophthalmoplegia was based on the location of the nerves within the cavernous sinus. The third cranial nerve was found to be the most vulnerable. Wray et al. stated that the sixth nerve in the cavernous sinus was the most concealed ocular motor nerve, so it was relatively rare to be associated with pituitary tumors [18]. In our study, seven patients had multiple ocular motor nerve palsies, and two had bilateral involvement, which may be attributed to the faster progression of pituitary metastases.

In our review study, decreased vision was present in 72.5% of patients. We found the patterns of visual field defects caused by PMs were diverse, in which mainly temporal visual field defects in both eyes were predominant but could also manifest as types of visual field defects, such as paracentral defects, central scotomas, visual field constriction, arcuate field defects. Unless pituitary apoplexy occurs, the slow progression of bitemporal visual field defects is usually caused by pituitary adenomas. Gan et al. showed a median of one year of presentation in patients with visual field defects in nonfunctioning pituitary adenoma [49]. We found a rapid deterioration of visual field defects in most patients with PM; 1/3 had an onset of less than a month. However, there was often a delay in diagnosis because 37.3% were initially diagnosed with pituitary adenoma. It, therefore, suggested that if a rapid visual field defect appeared, the patient might have a malignancy when there is no pituitary apoplexy.

Although there was no difference between the surgical and nonsurgical groups regarding the overall survival time of the patients [50], surgery can directly remove the compression of the optic chiasm and improve the visual disturbance. At the same time, it can confirm the pathological type of tumor, reduce the secretion of hormones, and provide a scheme for later treatment [44]. A recent study found that compared with observation, the survival of pituitary carcinoma was significantly better with surgery [51]. Further prospective studies are needed to evaluate the efficacy of radiotherapy, chemotherapy, and neurohormonal therapy. Surgical treatment improved visual acuity and visual field deficits in most patients. Still, it was not as effective for cranial nerve palsy, probably because of the complex structure of the cavernous sinus and the difficulty of isolation between the tumor and surrounding tissues. In our literature review, PM is mainly treated with transsphenoidal surgery, and 65% of patients had a survival time of fewer than six months. However, the sample size of this review was small, mainly based on case reports. From a symptomatic point of view, these patients dramatically improved their quality of life. Another limitation of this review is that we only used PubMed as our database and only included literature in English. Further research could include more data platforms and literature in other languages.

In conclusion, clinical history is essential for the differential diagnosis of PM, including age over 50 years, history of malignancy, clinical symptoms, and the pattern of rapid progression. For elderly patients with a pituitary tumor, PM should be on the list of differential diagnoses in which rapid progressive visual impairment, especially ocular motor nerve palsy, is present, combined with a prior history of cancer. We strongly recommend that all patients with pituitary tumors undergo a detailed neuro-ophthalmologic examination, including visual acuity, visual fields, and ocular motility. Although it does not improve patient survival, pituitary surgery may address the visual impairments to improve the patient's quality of life.

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Ethics statement

This study was approved by the Ethics Committee of Shanghai Renji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. Informed consent was not required for this retrospective study.

Data availability statement

Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

Hongliang Wang: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mingjie Zhu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Formal analysis, Data curation. **Yan Yan:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.heliyon.2024.e26027>.

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