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Case Report

Early and isolated breast cancer metastasis to the pituitary: A case report and systematic review

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ABSTRACT

Background: Pituitary metastases (PMs) arising from breast cancer tend to occur many years following initial diagnosis, and after other systemic metastasis have been identified. Survival is generally considered to be poor. However, there are cases where patients present with an isolated metastatic lesion in the pituitary. Survival in this subset of patients has not been evaluated. We present a case of isolated PM that presented two years after initial diagnosis of breast cancer. We performed a systematic review of 38 breast cancer patients with PM. We report presentation, treatment strategy, and outcomes of breast cancer metastasis to the pituitary and highlight cases of isolated PM.

Case Description: A 39 year old female presented with complaints of headache and polydipsia two years after diagnosis with breast cancer. Systemic workup was unremarkable, but brain imaging identified an isolated PM. Transsphenoidal debulking was performed with adjuvant radiation therapy (RT) targeted to the sellar region. Unfortunately, she passed away 9 months later from systemic progression.

Conclusion: A total of 38 patients were included systematic review. Of these, 13 had isolated PM. Prevalent signs/symptoms included visual disturbance, diabetes insipidus (DI), and hypothalamic dysfunction. Patients treated with surgical resection and adjuvant chemotherapy (ChT), or RT had better survival than those treated with resection alone. Patients that receive treatment for isolated PM may survive for many years without progression or recurrence.

Keywords: Breast cancer, Breast neoplasms, Pituitary gland, Pituitary metastasis, Pituitary neoplasms, Skull base

INTRODUCTION

Pituitary metastasis (PM) was first described by Ludwig Benjamin in 1857 and subsequently by Harvey Cushing in 1913.[8] The pituitary gland is an infrequent target of metastasis, as only 1% of sellar region neoplasms arise from malignant colonization.[52] Despite the rarity of PM, it has been increasingly described in the literature, likely due to improvements in neuroimaging and therapeutic strategies that have prolonged survival of cancer patients.

PM most commonly arises from breast cancer.[25,48] It is typically detected many years after diagnosis of the primary lesion, and after the tumor has already spread to multiple organs.[34] Common symptoms include polyuria and polydipsia, visual deficits, and hormonal disturbance.[25,48] Headache, nausea, vomiting, and fatigue are also common

and may be difficult to attribute to a *de novo* pituitary mass as they tend to occur in the setting of widespread disease,[4,20,25,34] and during ongoing chemotherapy (ChT) and/or radiotherapy (RT). Surgical intervention is typically indicated for symptom mitigation,[20,25,48] although survival is particularly poor when the lesion originates from breast or lung cancer.[48]

Here, we present the case of a patient with a solitary metastatic lesion at the pituitary gland detected only 2 years after diagnosis of invasive ductal carcinoma. A systematic review was performed with the aim of quantifying presentation and treatment outcomes in patients with PM stemming from breast cancer, which highlights cases where patients had isolated PM.

CASE REPORT

A 39-year-old woman was diagnosed with invasive ductal carcinoma in August 2018. She completed neoadjuvant therapy and then underwent total mastectomy in January 2019. The pathology report described invasive ductal carcinoma with marked treatment effect, in a background of extensive ductal carcinoma *in situ*. The tumor was immunopositive for estrogen receptor (ER), human epidermal growth factor receptor 2 (HER2) and immunonegative for progesterone receptor (PR). The patient was seen in clinic in July 2020 with new headache, unquenchable thirst, and diminished visual acuity of the left eye. A magnetic resonance image (MRI) demonstrated a 1.6 × 1.7 × 2.5 cm lesion on the pituitary stalk [Figures 1a-f]. Systemic workup yeilded no other sites of metastasis. Endocrine assessment revealed central adrenal insufficiency and central hypogonadism and was suggestive of hypothyroidism. There was no laboratory confirmation of diabetes insipidus (DI). A subtotal resection was acheived via transsphenoidal endoscopic surgery in August 2020, which was followed by adjuvant RT. Postoperatively, she developed transient DI necessitating treatment with desmopressin and was continued on exogenous glucocorticoids.

The patient was seen for follow-up in December 2020. She complained of bowel and bladder incontinence, which prompted MRI of the head and spine. While her residual tumor involving the stalk and hypothalamus had diminished in size, multiple intracranial areas of abnormal enhancement involving the cerebellum, brainstem, and supratentorial sulci were present [Figure 1g]. Leptomeningeal metastases were also seen in the spinal cord [Figure 1h]. In April 2021, she was diagnosed with hydrocephalus [Figure 1i]. A palliative ventriculoperitoneal shunt was placed, but she succumbed to the disease in May 2021. Immunohistochemical analysis of the PM revelaed positivity for ER, PR, and HER2 [Figures 2a-d].

LITERATURE REVIEW

Methods

Search strategy

We aimed to ascertain all peer-reviewed publications reporting PM arising from a primary breast cancer lesion. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline was employed to ensure quality, transparency, and completeness of our study.[40] A librarian was consulted to construct the search string, which included terms from two themes: (1) pituitary neoplasms and (2) breast neoplasms [Supplementary Table 1]. Terms were searched as both keywords and database subject heading as appropriate. Both adjacency operators and truncation were used to capture phrasing variations in keyword searching. No language or date restrictions were applied to the search.

Papers were collected through Ovid MEDLINE in February 2021. The search results are summarized in [Figure 3]. Conference papers/abstracts, studies not written in English, and studies that presented no primary data were excluded. After abstract review, 181 studies remained. These were then screened, and studies were included if they were case reports or case series of patients that had histologically confirmed breast cancer with metastasis to the pituitary. Postmortem studies and studies that lacked sufficient clinical data were excluded. There were 27 articles that met inclusion criteria. We then included five additional studies[7,9,10,45,55] found while cross referencing studies found in the initial search. Therefore, a total of 32 articles were used in the analysis. Abstract screening, full-text review, and data extraction were performed by a single author.

Data extraction

Data collected included: breast cancer subtype and histological features, clinical presentation, age at PM diagnosis, time between breast cancer diagnosis and PM, gender, hormonal profile, follow-up details, treatment modalities, disease progression, and overall survival. In cases where patients had breast cancer relapses, the time from first diagnosis to PM was reported. All endocrine diagnoses and laboratory values were reported before surgical resection of PM. Resections were considered to be total resections unless specifically stated otherwise (partial resection or debulking). Descriptive statistics were presented for variables and expressed as mean ± S.E.M.

RESULTS

Patient characteristics and presentation

Our literature search identified 32 studies with histologically confirmed PM from breast cancer. Including our patient,

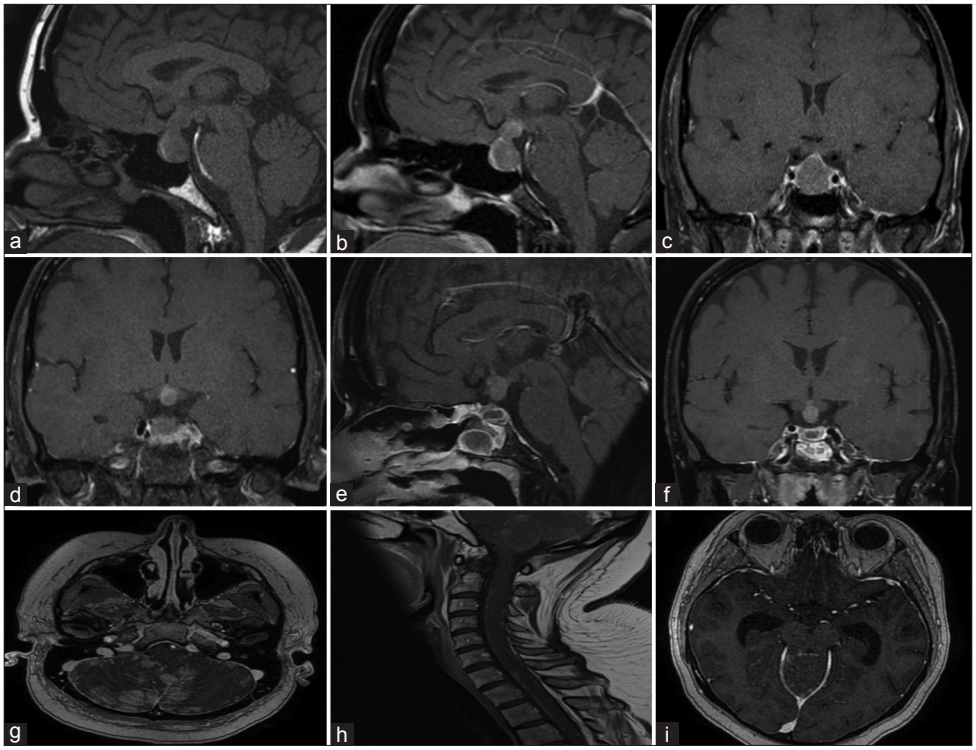

Figure 1: MRI showing PM and. (a-d) Preoperative coronal and sagittal T1 MRI with and without contrast showing a lesion in the pituitary stalk and gland. There is mild splaying of the optic chiasm with lateral displacement of the left optic nerve. (e and f) A residual tumor involving the stalk and hypothalamus was identified on postoperative coronal and sagittal T1 MRI with contrast. (g and h) A follow-up MRI of the brain and cervical spine with contrast showed a leptomeningeal metastatic disease. (i) A follow-up MRI of the brain with contrast showing hydrocephalus due to leptomeningeal disease. A palliative ventriculoperitoneal shunt was placed.

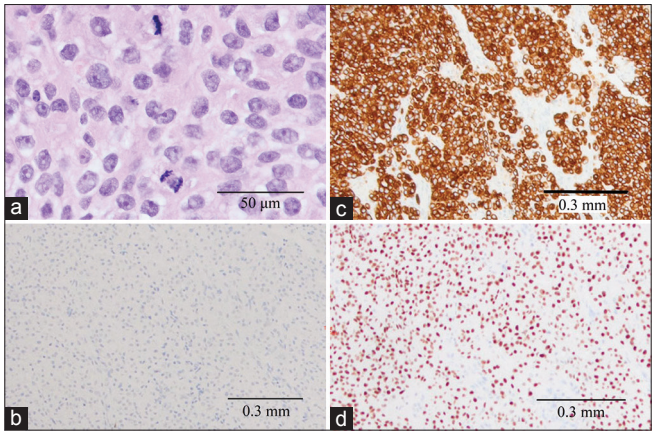

Figure 2: Histological appraisal of PM. (a) Hematoxylin and eosin stained section demonstrating neoplastic cells with anaplastic nuclei, prominent nucleoli, and mitotic activity. (b) Cytokeratin 7 immunohistochemically stained section showing strong, diffuse cytoplasmic immunopositivity. (c) Cytokeratin 20 immunohistochemically stained section showing immunonegativity. (d) Gata3 labeled section showing strong nuclear positivity.

38 patients were included in the analysis. The data are summarized in Table 1, with detailed description of the extracted data in Table 2. Patients were diagnosed with PM at a mean age of 59 years (range 30–93 years). The median time from breast cancer diagnosis to PM was 60 months (mean 74 months, range 0–228 months) based on available data from 29 of 38 patients. Interestingly, the pituitary lesion was discovered before breast cancer diagnosis in five cases. The PM was the only metastatic lesion in 13 cases.

Visual field deficits and decreased visual acuity were the most common presentations, occurring in 21 and 16 patients, respectively. Polyuria or polydipsia was reported in nine patients, and DI was confirmed in six of nine patients with available data. Other common symptoms included headache (17), nausea and vomiting (5), and fatigue (4). There were three patients whose only presenting complaints were headache, nausea, or fatigue. Ophthalmoplegia was reported in six patients. Anterior pituitary function was disrupted in all but three cases with available hormonal data (29/32). The gonadal hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were most affected, and hyposecretion was noted in 15 of 16 cases that reported hormonal values. We assessed triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH). Hypothyroidism was noted in 8 of 11 patients with reported values for TSH and thyroid hormones. One patient had

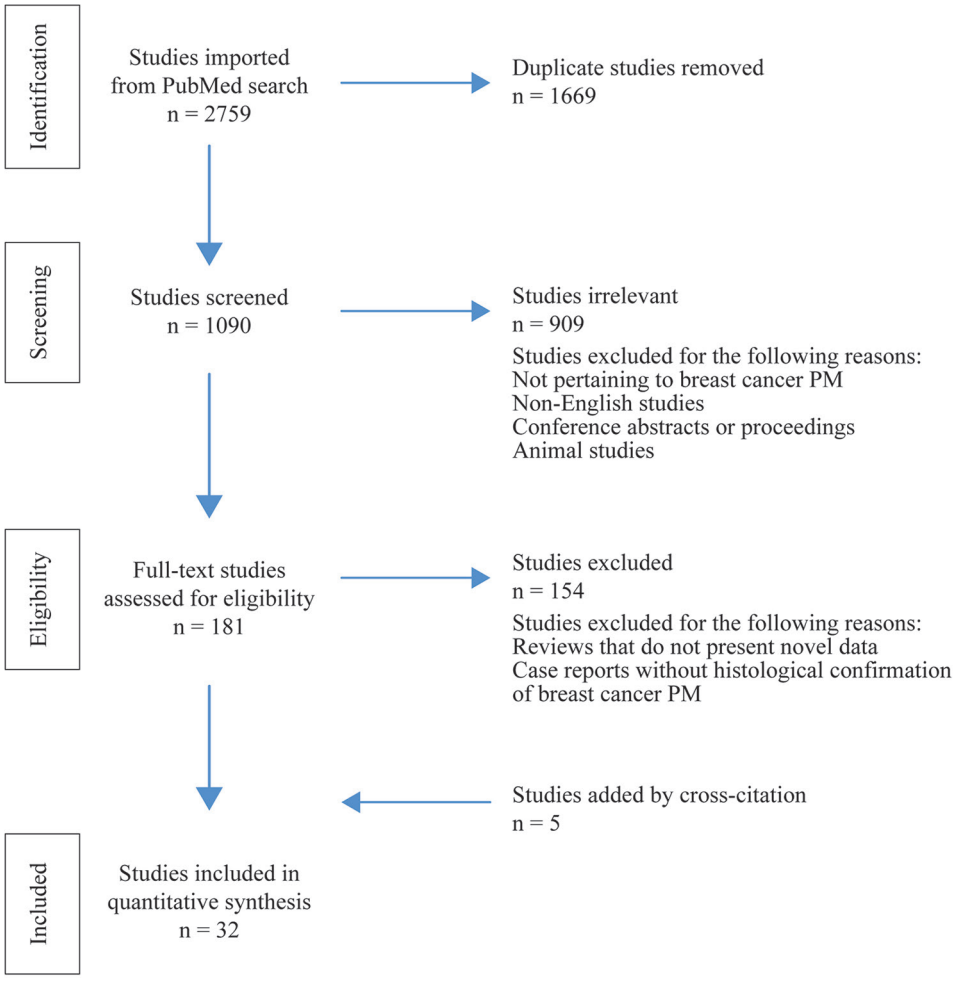

Figure 3: PRISMA flowchart for literature review.

primary hypothyroidism before PM diagnosis which was not included. Hypocortisolism was reported in 10 of 15 cases that assessed function of the hypothalamic-pituitary-adrenal axis. Hyperprolactinemia was found in nine of 15 cases that reported prolactin levels.

Additional sites of metastasis

The majority of patients had additional metastatic sites at the time of PM diagnosis. Data on burden of metastatic disease were available in 35 cases, and 22 were found to have additional metastatic lesions at the time of PM diagnosis. Metastasis to bone and lung were the most common, occurring in 13 and 10 patients, respectively. Other sites included lymph nodes (6), liver (4), adrenal gland (3), thyroid (2), thoracic wall (1), and opposite breast (1). There were only three cases that reported central metastasis in addition to PM. Of the nine patients diagnosed with PM within 24 months of initial breast cancer diagnosis, four had additional systemic metastases.

Histological features

The majority of PMs were reported from primary invasive ductal carcinoma (17/25 cases that specified histological class). Notably, there were four cases of mucinous carcinoma, a relatively rare type of breast cancer. We then quantified the prevalence of hormonal receptor expression in PM. Expression profiles of ER, PR, and HER2 has prognostic implications and help guide treatment in patients with breast cancer.[7] Histological appraisal of the primary breast cancer lesion was reported in selected cases. Expression of ER was seen in 16 of 22, 10 of 20 expressed PR, and 10 of 17 expressed HER2. There were no cases of triple-negative breast cancer among the cases that reported expression of all receptors.

Treatment and outcomes

Follow-up was available for 27 of 38 cases at a mean of 15 months after PM diagnosis [Table 2]. Eleven patients were deceased following treatment, and mean time to death was 7 months (range 0–16 months). Operative resection was performed in 29/38 cases, and only partial resection was achieved in 13 cases. Follow-up was provided in 10/13 patients that received partial resection, and five were alive at 7 months follow-up (range 0-18 months). The addition of RT may be associated with improved survival. In seven cases where adjuvant RT or RT+ChT was employed, five patients were alive without PM progression. However, all patients that did not receive adjuvant RT (resection alone or only ChT) were deceased (3/3). One patient had additional CNS involvement, and two rapidly deteriorated after surgery. Total resection of PM is challenging, and patients are often left with residual disease. For this reason, adjuvant therapies are often employed. We compared survival between patients receiving RT (either RT alone or in addition to ChT) and those that underwent surgery without RT or that had ChT alone [Figure 4a]. There were 16 cases where full resection was achieved, and follow-up results were reported in 12. Eight patients were alive at a mean of 23 months (range 3–132 months). Adjuvant therapies were used in 9/12 cases that reported follow-up and seven patients were alive. In the remaining three cases that did not employ adjuvant therapy, two were deceased (one had PM recurrence at 2 months, and then received CyberKnife and ChT.[45] One was live with stable systemic disease at 12 months). Finally, there were five patients with widespread disease that received RT or ChT without surgical intervention (histological confirmation

Table 1: Characteristics of reported cases of PM from breast carcinoma.

Number of cases	***n*=38**
Sex	
Female	38
Mean age (years ± S.E.M)	59±2.1
Mean time from breast cancer diagnosis to PM (months ± S.E.M)	74±12
Clinical presentation	*n*=36
Visual field deficits	21 (47%)
Diminished visual acuity	18 (53%)
Headache	17 (47%)
Nausea and vomiting	5 (15%)
Fatigue	4 (12%)
Ophthalmoplegia	5 (15%)
Polyuria/polydipsia	9 (26%)
Hormonal disturbance	
LH	15/16 (94%)
FSH	15/16 (94%)
TSH	11/13 (85%)
Cortisol	11/15 (73%)
GH	3/7 (42%)
Diabetes insipidus	8/13 (62%)
Hyperprolactinemia	11/14 (79%)
Patients with isolated PM	13/35 (37%)
Patients with reported metastasis	*n*=22
Bone	13 (65%)
Lung	10 (50%)
Lymph nodes	6 (30%)
Liver	4 (20%)
Adrenal glands	3 (15%)
Thyroid	2 (10%)
Thoracic wall	1 (5%)
Opposite breast	1 (5%)
Pericardium	1 (5%)
PM as first manifestation of malignancy	5
Histopathology	*n*=25
Invasive/infiltrating ductal carcinoma	17 (68%)
DCIS	4 (16%)
Mucinous	4 (16%)
Receptor expression	
ER	16/22 (72%)
PR	10/20 (50%)
HER2	10/17 (59%)

PM: Pituitary metastasis, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, ER: Estrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2

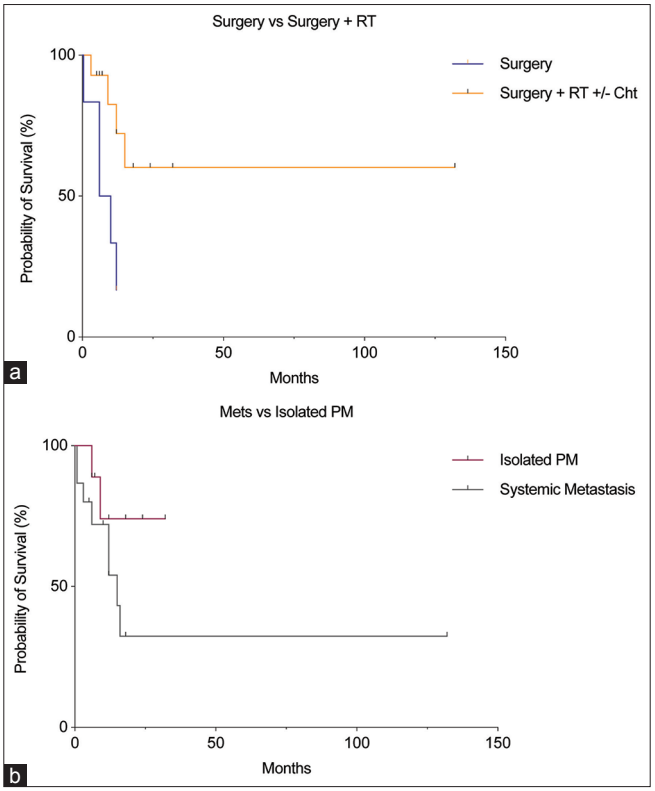

Figure 4: Kaplan–Meier representation of survival. (a) Comparing overall survival with and without adjuvant RT. (b) Comparing overall survival between isolated PM and patients with peripheral metastasis. PM: Pituitary metastases, RT: Radiation therapy, ChT: Chemotherapy.

Table 2: Cases of PM from breast carcinoma.

References	Year	Age/sex	Location	Presentation	Hormonal disturbance	Time from initial DX to pituitary metastasis (months)	Histopathology breast CA	PM tumor markers	Other CNS/ systemic metastasis	Management	TTR (months)	FU period (months/outcome)
Present case	2021	39/F	Sellar and suprasellar	N/V, weight loss persisting thirst, decreased acuity	AHP	24	DCIS	ER+, PR+, HER2+	None	Partial resection, RT	4 - Residual PM. CNS and systemic progression	9 – Deceased.
Cai *et al.*[4]	2019	57/F	Left sellar, pituitary stalk	Headache, bitemporal hemianopsia, hyperprolactinemia	AHP	192	DCIS	ER+, HER2+	None	Resection	No pituitary recurrence	12 – NED
Magalhães *et al.*[37]	2014	54/F	Stalk	Blurred vision and diminished visual acuity	AHP	120	Invasive ductal carcinoma	ER+	Bone, lung	Partial resection, RT	Progression not reported	5 – Alive. Disease stable
Spinelli *et al.*[57]	2012	72/F	Sellar	Bitemporal hemianopsia	AHP	148	Infiltrating ductal carcinoma	ER+, PR+	Bone	Subtotal resection	Residual PM	0 – Deceased. Rapid deterioration following surgery
Ravnik *et al.*[49]	2016	57/F	Sellar	Headache, trochlear nerve palsy,	AHP	NR	Glandular breast carcinoma	ER+, PR+	Bone, lung	Partial resection, RT, ChT	No progression	12 – Alive. Disease course stable
Lin *et al.*[36]	2007	37/F	Stalk	Polyuria and polydipsia	AHP, DI	72	Infiltrating ductal carcinoma	ER+, PR+, HER2+	Liver, bone	RT	No pituitary recurrence	10 – Alive.
Kam *et al.*[29]	2017	63/F	Stalk	Polyuria and polydipsia	AHP, DI	60	Invasive ductal carcinoma	ER+, PR−, HER2+	None	Resection, RT	No pituitary recurrence	6 – NED
Fortunati *et al.*[21]	2015	83/F	Suprasellar extension	Visual disturbance, weakness	AHP, DI	0	Infiltrating mucinous carcinoma	NR	None	Resection	No pituitary recurrence	12 – Alive. Initial breast lesion remains stable. No metastases.
Mills *et al.*[39]	2018	65/F	Sellar	Headache, visual field disturbance, decreased acuity	NR	NR	Breast cancer – not specified	NR	Lung. CNS – cerebellar, frontal lobe, temporal lobe	Partial resection, ChT	Residual PM	0.4 – Deceased
Kim *et al.*[33]	2012	65/F	Stalk	Bitemporal hemianopsia, decreased visual acuity in the left eye	AHP	60	Invasive ductal carcinoma	NR	Thoracic wall, bone	Partial resection, CyberKnife. No residual mass	No pituitary recurrence	5 – Alive. No recurrence of PM.
Park *et al.*[46]	2016	43/F	Sellar	Headache, weakness, somnolence	AHP, DI	17	Invasive ductal carcinoma	ER+, PR−, HER2+	None	Partial resection, RT, ChT	3 – progression. Treated with ChT.	7 – Alive. PM decreased in size.

(Contd...)

Table 2: *(Continued).*

References	Year	Age/sex	Location	Presentation	Hormonal disturbance	Time from initial DX to pituitary metastasis (months)	Histopathology breast CA	PM tumor markers	Other CNS/ systemic metastasis	Management	TTR (months)	FU period (months/outcome)
El Habnouny *et al.*[17]	2020	66/F	Intra- and supra-sellar	Headache, oculomotor paralysis	AHP	NR	Invasive ductal carcinoma	ER+, PR+, HER2–	NR	ChT, RT	NR	7 – Alive, but disease status not reported
Eksi *et al.*[16]	2014	56/F	Supra-sellar	Headache, decreased visual acuity	Normal hormonal profile	84	Infiltrating ductal carcinoma	ER–, PR–	None	Resection, gamma-knife	NR	NR
Castle-Kirszbaum *et al.*[6]	2020	51/F	Sellar	Bitemporal hemianopsia, malaise	AHP	NR	Invasive ductal carcinoma	ER+, PR–, HER2–	Oligometastatic sites – including intracranial	Resection	NR	NR
Nose.[43]	2019	70/F	Not specified	Headache, bitemporal hemianopsia, diplopia, malaise	AHP	144	Breast carcinoma – not specified	ER–, PR–, HER2+	Bone, hilar nodes, adrenal, lung	RT, ChT	NR	16 – Progression of systemic disease and death
Khandwala *et al.*[30]	2004	60/F	Anterior pituitary	Fatigue, vomiting	AHP	144	Infiltrating ductal carcinoma	ER–, PR–, HER2+	Bone, lung	Resection	NR	NR
Ersoy *et al.*[19]	2007	55/F	Sellar	Bitemporal hemianopsia, polyuria, polydipsia	AHP, DI	62	Infiltrating ductal carcinoma	NR	Opposite breast	Partial resection, GammaKnife	Residual PM. Progression not reported	12 – Deceased
Verhelst *et al.*[58]	1995	58/F	Sellar	Bitemporal hemianopsia	AHP	228	Ductal carcinoma	NR	Supraclavicular nodes	Resection, RT	No pituitary recurrence	18 – No progression
Cardona-Rovira *et al.*[5]	2019	51/F	NR	Bitemporal hemianopsia	AHP	NR	Infiltrating ductal carcinoma	NR	Bone, lymph nodes	Resection, RT	NR	NR
Ozkan[45]	2011	53/F	Sellar	Polyuria, polydipsia, fatigue, headache	AHP, DI	48	Infiltrating ductal carcinoma	ER–, PR–, HER2+	Liver, bone	Resection	2 – PM recurrence – treated with CyberKnife	12 – Deceased – progression of liver Mets.
ŞiMşek[55]	2020	61/F	NR	Headache	NR	0	Mucinous breast cancer	ER+ PR+, HER2–	Adrenal, lung	Resection, ChT, RT	No pituitary recurrence	132 – Alive. Recurrence of breast lesion at 86 months.
Chuang and Tsai[10]	2018	63/F	Sellar	Decreased acuity, visual field defects	AHP	180	Invasive mucinous carcinoma	ER+, PR+	None	Resection, ChT	No pituitary recurrence	32 – NED

(Contd...)

Table 2: *(Continued).*

References	Year	Age/sex	Location	Presentation	Hormonal disturbance	Time from initial DX to pituitary metastasis (months)	Histopathology breast CA	PM tumor markers	Other CNS/ systemic metastasis	Management	TTR (months)	FU period (months/outcome)
Aaberg *et al*[1]	1994	68/F	Sellar	Visual deficits	NR	48	Breast carcinoma – not specified	NR	Bone	Resection	NR	2 – Alive
Gilard *et al.*[22]	2016	47/F	Sellar	Bitemporal hemianopsia, decreased acuity	DI	28	DCIS	HER2+, PR–	None	Resection	NR	6 – Deceased – systemic progression
Gilard *et al.*[22]	2016	57/F		Headache, polyuria, polydipsia	AHP	60	DCIS	ER2+, HER2+	Bone, cervical lymph nodes	Resection, RT	No Recurrence	15 – Deceased – systemic progression
Witczak *et al.*[59]	2013	67/F	Sellar	Poor visual acuity, headaches, ocular nerve palsy	AHP	0	Infiltrating ductal carcinoma	NR	Lung	Resection	NR	3 – Deceased
Senetta *et al.*[53]	2015	82/F	Sellar	Headache, visual field defect	AHP	0	Mucinous neuroendocrine breast cancer	ER+, PR+, HER2–	NR	Resection	NR	NR
McCormick *et al.*[38]	1989	38/F	Sellar	Increased lactation, visual field defect	NR	0	Diffuse infiltrating carcinoma	NR	None	Resection, RT	NR	Alive – time not reported
McCormick *et al.*[38]	1989	93/F	Sellar	Decreased visual acuity, visual field deficits	AHP	36	Breast carcinoma	NR	Pulmonary nodules – not confirmed mets	Resection, RT	NR	NR
Zager and Hedley-Whyte.[60]	1987	56/F	Sellar	Headache, nausea, vomiting, CNVI palsy	NR	24	Infiltrating ductal carcinoma	ER+	Axillary lymph nodes, bones, lung, liver, adrenal glands	RT	NR	0.75 – Deceased
Duvall and Cullen[15]	1982	76/F	Sellar	Bitemporal hemianopsia, decreased acuity	NR	36	Breast carcinoma	NR	Thyroid	Partial resection	4 – No pituitary recurrence. New Cerebral and skeletal metastasis	6 – Deceased
Murata *et al.*[42]	2003	61/F	NR	Polyuria, polydipsia	DI	>24	Breast carcinoma	NR	liver, bone, cervical nodes, lung	ChT	PM present	18 – Alive – pituitary mass diminishing
Gołkowski *et al.*[24]	2006	52/F	Sphenoid	Fatigue	AHP	120	Breast carcinoma	NR	None	Partial resection, RT	Residual PM. Decreased in size after RT	18 – Alive. Disease stable

(Contd...)

Table 2: *(Continued)*.

References	Year	Age/sex	Location	Presentation	Hormonal disturbance	Time from initial DX to pituitary metastasis (months)	Histopathology breast CA	PM tumor markers	Other CNS/ systemic metastasis	Management	TTR (months)	FU period (months/outcome)
Chu *et all*.[9]	2016	60/F	Sellar	Bilateral hemianopsia, decreased acuity	AHP	180	Infiltrating ductal Carcinoma	ER+, PR+, HER2−	None	Resection, RT	No recurrence	24 – Survived 24 m without relapse
Castle-Kirszbaum *et al*.[13]	2018	30/F	Sellar	CNIII palsy, visual field deficit, headache	Normal hormonal profile	NR	Breast carcinoma	ER−, PR−, HER2+	Known metastatic disease – locations not specified	RT, ChT	NR	NR
Castle-Kirszbaum *et al*.[7]	2018	61/F	Sellar/suprasellar	Headache, DI	AHP, DI	NR	Breast carcinoma	ER+, PR+, HER2+	Known metastatic disease – locations not specified	RT	NR	NR
Castle-Kirszbaum *et al*.[7]	2018	61/F	Sellar/suprasellar	Visual field defect	AHP, DI	NR	Breast carcinoma	NR	None	RT, ChT	NR	NR
Castle-Kirszbaum *et al*.[7]	2018	66/F	Sellar/suprasellar	Visual field defect	AHP, DI	NR	Breast carcinoma	NR	None	RT	NR	NR

M: Male, F: Female, NR: Not reported, RT: Radiation therapy, m: Month, NED: No evidence of disease, FU: Follow-up, N/V: Nausea and vomiting, DCIS: Ductal carcinoma in situ, TTR: Time to recurrence, AHP: Anterior hypopituitarism, DI: Diabetes insipidus, ChT: Chemotherapy, PM: Pituitary metastasis, ER: Estrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2

performed postmortem or by biopsy). Mean follow-up from these patients was 11 months (range 1–18 months). One patient receiving ChT showed diminishing size of PM at 18 months and one receiving RT had stable disease at 10 months. Two were deceased, and one was alive, but disease status was not reported.

Assessing the effectiveness of treatments targeted to PM can be confounded by systemic disease. Patients with isolated PM had better outcomes compared to those with systemic metastases [Figure 4b]. There were 21 PM cases with preexisting metastasis, and follow-up was reported in 16 cases at a mean of 16 months (range 0–132 months). Only seven of 16 patients were alive at follow-up. Of seven patients with isolated PM that had complete resection, six were alive without recurrence or progression at 15 months follow-up (range 6–32 months). Of 5/7 patients that received adjuvant therapy, 4/5 were confirmed to be alive, and one patient's status was unclear. Two patients did not receive adjuvant therapy; one was deceased at 6 months from systemic progression, and one was alive without PM recurrence. Subtotal resection was achieved in four cases of isolated PM, and all received adjuvant ChT or RT. Follow-up was reported in three patients. Two patients were alive at 11 months follow-up (range 7–18 months) with stable disease.

DISCUSSION

Our review included data from 38 patients with confirmed breast cancer metastasis to the pituitary. The most common primary tumor was invasive ductal carcinoma. Interestingly, there was a high proportion of mucinous breast cancers (16%), which is higher than the 2–3% reported among all breast cancers.[2] The majority of patients were diagnosed several years after initial diagnosis of primary breast cancer and had at least one other metastatic site at diagnosis. The presence of additional metastases has been described as the best predictor of long-term outcome,[25] which is supported by our results, as 7/1l patients with isolated PM were alive at follow-up, compared to 5/16 with systemic disease. Isolated PM was relatively common (13/35). This was unexpected as PM is typically described as occurring late into the disease course, and well after other metastatic sites have been established.[4] The prognosis appears to be favorable in these patients as the majority of patients survived many years after resection with adjuvant RT.

Metastases to the pituitary may present insidiously, and many are found incidentally on autopsy.[34] Features suggestive of PM include the tendency for neurohypophysis involvement, rapid growth rate, and DI.[48] Visual field deficits, such as bitemporal hemianopsia, or progressive decline in visual acuity are common manifestations. However, PM may also present with nonlocalizing symptoms, such as headache, nausea, and fatigue. In our analysis, 18 patients suffered from nonlocalizing symptoms, and three of these did not have concomitant visual symptoms or polyuria/polydipsia that may aid in localizing a pituitary lesion. The clinical presentation in our review is similar to a large cohort of patients with PM arising from different organs.[48] The cohort included 85 patients with PM treated at the Memorial Sloan Kettering Cancer Center; they found 62% of patients presented with visual deficits, 31% with cranial nerve palsy, and 28% with DI.[48]

Hormonal disturbance is a common complication in PM. Particularly, DI has been reported in up to 70% of symptomatic PM.[38] Polyuria and polydipsia were described in 26% of patients and were confirmed in 62% of patients from reports that formally assessed for DI (8/13). Another common feature of PM is hormonal disturbance.[54] Dysfunction of at least one anterior pituitary hormone signaling system was present in all but three cases where pituitary function was reported. Hyperprolactinemia was found in 79% of cases that assessed prolactin levels (11/14). Interestingly, FSH and LH were the most common hormones affected. This is seemingly advantageous for patients as many breast cancers thrive on ER activity.

Breast cancer is the most common malignancy in women and is a frequent source of PM.[26,48] This region may be particularly enticing to circulating breast cancer cells due to the hormonal gradient surrounding the pituitary. [18,20,25] The superior and inferior hypophyseal arteries supply the infundibulum and posterior pituitary, respectively,[11] and provide a route for hematogenous spread of liberated cancer cells.[4] Breast cancer cells have been shown to express receptors for FSH and LH.[35,51] High levels of FSH and LH, such as those seen in postmenopausal women, facilitate migration and invasion through phosphorylation of focal adhesion kinases and actin-binding proteins, which endow the ability to traverse through tissues.[51] Prolactin promotes proliferation and survival and also enhances motility of breast cancer cells.[12,13] In addition, although the capillaries comprising the median eminence and neurohypophysis (and other circumventricular organs) contain components that form the blood brain barrier (BBB), they are relatively porous to allow for the passage of molecules required for endocrine signaling.[27,31,41] Together, these factors may make the pituitary an ideal destination for circulation breast cancer cells.

Breast cancers that express HER2 are more aggressive and frequently spread to the CNS. In our study, HER2 was positive in 10/17 (58%) of cases that reported HER2 expression in the primary breast lesion. This is higher than the reported prevalence of HER2 positivity in primary breast cancers of 15–30%,[18,50,28] suggesting that HER2 + cancers have a predilection for targeting the pituitary. Some propose this may be due to the use of monoclonal antibodies directed toward HER2-positive breast cancers, which hinder systemic

progression,[56] but leaves the CNS as a haven for malignant. Interestingly, there were no PM arising from triple-negative breast cancer, which commonly invades the CNS.[47]

There was a trend toward improved local control and survival in patients treated with adjuvant RT. This was particularly true following partial resection. There was only one case of PM recurrence, which followed total resection in a patient that did not receive adjuvant therapy. In a large cohort of patients with PM, 76% received RT (whole-brain radiotherapy or local RT), 21% received surgery, and within the surgical group, the majority also received neoadjuvant or adjuvant RT. There was an association between surgical resection and prolonged survival; however, this may be due to selection of patients with severe symptoms and good functional status.[48] For patients who are not candidates for surgery, stereotactic radiosurgery (SRS) appears to be a promising option. Benjamin *et al*. reported that SRS resulted in excellent local control and symptom improvement in five patients with PM in whom surgery was not feasible.[3]

New strategies for treating cancer metastasis to the CNS are being investigated. Various immune checkpoint inhibitors (ICIs) circumvent the malignant cell's immune evasive mechanisms[44] and show promise in treating PM. A recent case report of PM arising from melanoma showed that pembrolizumab, an ICI targeting programmed death 1 (PD-1), markedly decreased PM size within 4 months of starting treatment.[23] In addition, strategies aimed at increasing BBB permeability may be used in conjunction with antibody therapy to further enhance central access and improve efficacy.[14,32] Tyrosine kinase inhibitors (TKIs) offer another avenue for treating HER2-positive breast cancers. A case report showed that the TKI, lapatinib, combined with capecitabine, diminished the size of breast cancer PM.[46] Therefore, these novel therapies show promise in treating PM, and further studies will be beneficial in elucidating how they may be integrated into existing treatment regimens.

CONCLUSION

Several patients in our analysis were diagnosed with isolated PM, and many survived without progression or recurrence for years after treatment. The presence of additional metastatic sites has the largest influence on survival. Patients that underwent resection combined with adjuvant ChT + RT or RT alone, whether they had isolated PM or multiple metastatic sites, had better survival than those with resection alone. Therefore, the data suggest that surgical resection combined with RT.

Limitations

The strength of conclusions is limited by the small number of cases. Furthermore, case reports are typically composed to reveal remarkable occurrences aimed to inform on a particular disease phenomena and may not necessarily reflect the typical sequelae in the natural history of a disease. Therefore, as case reports were used to compile the data in our analysis, the sample population may not be entirely representative. However, age at diagnosis, survival, and relative frequency of metastasis to different sites were all similar to that reported from larger studies. Another limitation is the lack of standardization among case reports. Subsequently, we could only quantify parameters based on the available data presented in each report. We also acknowledge that our findings regarding survival following surgical resection with or without adjuvant therapies may be subject to bias as patients who are selected for surgery are healthier with good functional status.

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Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY TABLE

Table S1. Final search strategy

Database: Ovid MEDLINE(R)
Search Strategy:

#	Searches
1	Breast Neoplasms/
2	((breast or mammary) adj2 (cancer* or neoplasm* or carcinoma* or tumor* or tumour*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3	1 or 2
4	Pituitary Neoplasms/
5	((pituitary adj5 (metasta* or cancer* or neoplasm* or carcinoma* or tumor* or tumour*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6	6, 4, or 5
7	7, 3, and 6