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Pituitary and other sellar region metastases

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Introduction

Metastases in the sellar region, which includes the pituitary gland, the pituitary stalk, and surrounding structures, have been interchangeably referred to as "sellar metastasis" or "pituitary metastasis" in the English literature. Those lesions account for less than 1% of sellar masses and autopsy studies estimate their prevalence in patients with known malignancy between 0.9% and 3.6% [1,2]. Their rarity may explain and excuse the widespread use of the term "pituitary metastasis" meaning any metastatic lesion in the sellar region but not necessarily in or restricted to the pituitary gland. We chose to use the term sellar metastasis (SM) for its broader anatomical meaning.

Usually, patients with SM have a known malignant disease with systemic dissemination, but the sellar lesion may also be the first manifestation of malignancy [3]. The first SM described was a pituitary melanoma found at autopsy in 1857 [4], and thereafter more than 500 cases have been reported in the English literature. In recent years, there has been a remarkable increase in reports on SM, which seems to result from longer survival of oncological patients, regular use of MRI and positron emission tomography-computed tomography (PET-CT) in cancer staging, and increased awareness of that condition [5]. The aim of this paper is to provide a concise but efficient review on this increasingly important subject.

Anatomical considerations

The posterior pituitary lobe and the pituitary stalk are both more commonly affected by metastatic lesions than the anterior lobe of the pituitary or other structures of the sellar region. That is likely due to the systemic arterial supply that reaches the posterior lobe and the pituitary stalk through the perforators of the internal carotid artery [2,6]. In addition, the posterior pituitary lobe has a broad area in contact with the sellar bone, and tumors with tendency for metastasizing to bone such as thyroid, renal, and prostatic cancers, could spread through this route. In contrast, the anterior pituitary lobe does not receive its blood supply from the systemic circulation but from the portal venous system descending from the hypothalamus [2,6]. Occasionally, a pituitary metastasis can be found concomitantly with or within a pituitary adenoma in the anterior lobe ("collision tumour"). In that case, the metastasis may have reached the anterior lobe of the pituitary through the arterial blood supply to the adenoma [7].

Pathology

Overall, metastasis typically occurs in older patients in the sixth to seventh decades of life with no evident sexual predominance [6]. The most frequent metastases to the sellar region are from breast and lung cancers, together comprising nearly 60% of cases [1,6,8], followed by kidney, prostate, and thyroid malignancies, each one contributing with nearly 5% (Table 1). In general, the frequency of sellar metastases may reflect the prevalence of the primary malignancies in the general population. However, the prevalence of sellar metastases at autopsy in breast cancer patients is nearly 30% [9], which makes the probability of having a SM higher than any other sellar lesion in a female patient who has had or currently has breast cancer [1,9]. When only surgically confirmed cases are considered, the most frequent sellar metastases are, in decreasing order of frequency, from breast, lung, and thyroid cancers in women, and lung, kidney, and liver cancers in men [3].

Diagnosis

Sellar metastases are symptomatic in only 7% of patients [10]. Usually, they are found in oncological patients undergoing MRI and/or PET-CT scans for disease staging and patients usually have other metastatic lesions when a SM is found [11,12]. On the other hand, SM can be the presenting symptom of malignancy in 20–40% of cases [3,6]. Therefore, the clinical diagnosis of a SM involves a high degree of suspicion, whereas a definite diagnosis, when necessary, requires biopsy of the lesion.

Table 1

Primary malignancy origin of 514 reported sellar metastases.*

Primary site	N	Percentage	Primary site	N	Percentage
Breast	182	35,4	Paranasal sinus	3	0,6
Lung	119	23,2	Oral Cavity	3	0,6
Renal	29	5,6	Germ cell Tumor	3	0,4
Prostate	25	4,9	Larynx	2	0,6
Thyroid	19	3,7	Ovary	2	0,4
Colon	17	3,3	Thymus	2	0,2
Melanoma/Skin	15	2,9	Salivary Glands	2	0,2
Unknown	13	2,5	Ileum	1	0,2
Stomach	12	2,3	Retroperitoneum	1	0,2
Liver	10	1,9	Bile Duct	1	0,2
Pancreas	7	1,4	Lymphosarcoma	1	0,4
Pharynx	7	1,4	Penis	1	0,2
Urinary/Bladder	7	1,4	Nasal Cavities	1	0,4
Endometrium	6	1,2	Merckel Cell carcinoma	1	0,2
Uterine/Choriocarcinoma	6	1,2	Ewing Sarcoma	1	0,2
Leukemia	5	1,0	Lipossarcoma	1	0,2
Lymphoma	5	1,0	Rhabdomiosarcoma	1	0,2
Multiple myeloma	3	0,6	**Total**	514	

*Reports were searched using Mendeley version 1.17.13 (2018) for windows remote search model on PubMed. The key words on all fields were "pituitary metastasis", "sellar metastasis", "metastatic cancer pituitary", "metastatic cancer sellar", "metastatic carcinoma sellar". The combination of "metastasis" and "pituitary" or "sellar" in the title was also used. References of retrieved papers was also searched for missing citations. Only papers in English were used. To update from the last review on this subject (He), we included reports from July 2013 to May 2018, except for a prevalence study based on questionnaires [13]. Papers not describing the primary site of malignancies were not included.

The most common presenting symptoms of SM are due to compression and/or invasion of surrounding structures such as cranial nerves, pituitary gland, pituitary stalk, and hypothalamus. Various combinations of signs and symptoms such as visual field defects, headache, ophthalmoplegia, diabetes insipidus, anterior hypopituitarism, and hyperprolactinemia are usually present at diagnosis in those few symptomatic patients [3,6,9]. Characteristically, SM show a more rapid growth and invasion of surrounding structures than most other lesions of the sellar region. The severity of symptoms determined by SM has been explained by the rapid growth of the lesion, obstruction of blood flow within the portal vessels with ischemic necrosis of the anterior pituitary, and invasion and/or destruction of the median eminence [3].

Diabetes insipidus, which is rarely seen in patients with more common anterior pituitary lesions such as adenomas, is frequently observed in patients with SM involving the pituitary stalk/hypothalamus [1,6,8,13–15]. Anterior pituitary hormone deficiencies are also more prevalent and severe in patients with SM, and mild/moderate hyperprolactinemia is present in nearly 80% of patients [3]. The aggressive behavior of SM leads to the rapid development of visual impairment demanding prompt diagnostic and treatment decisions [16]. Sellar metastasis should always be suspected in patients presenting with sellar masses, abnormal eye motility and/or diabetes insipidus, even without a known malignancy [3,6,8].

More recently, CTLA-4 blocking antibodies and anti-PD-1 antibodies used to treat some advanced types of cancer have been shown to cause hypophysitis, creating an additional challenge in the differential diagnosis of pituitary lesions in oncological patients as discussed below.

Hypophysitis induced by CTLA-4 blocking antibodies and anti-PD-1 antibodies

In addition to their antitumor effects, CTLA-4 inhibitors and anti-PD-1 antibodies also trigger a wide range of autoimmune side effects including hypophysitis. Ipilimumab-induced hypophysitis occurs in 10–17% of patients, typically after 2–3 months of treatment [17–19]. Symptoms include headache, fatigue, hyponatremia and one or more anterior pituitary deficiencies, notably central hypothyroidism, followed by hypoadrenalism and hypogonadism. Hyperprolactinemia, growth hormone deficiency and diabetes insipidus are much less common. Sellar MRI shows a mild/moderate homogeneous or heterogeneous pituitary enlargement, with strong contrast-enhancement, with or without stalk thickening. Those radiological abnormalities usually revert in 6–8 weeks after drug suspension [19,20]. Pretreatment pituitary MRI and monthly FT4 and TSH measurements have been recommended in patients receiving Ipilimumab. The medication should be interrupted if compressive effects occur [21]. Hormonal deficits can recover after drug suspension at variable time intervals, except for