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1 **Pituitary Metastasis of Malignant Melanoma misdiagnosed as Pituitary Adenoma: a case report and**
2 **systematic review of the literature.**

3 **Métastase hypophysaire d'un mélanome malin mimant un adénome hypophysaire : un case report et une**
4 **revue systématique de la littérature**

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8

9 **Abstract**

10

11 We report a case of malignant melanoma revealed by a metastasis to the pituitary gland. The tumor was
12 misdiagnosed as a pituitary adenoma and aggressive transsphenoidal surgery was complicated by a cerebrospinal
13 fluid fistula. Nine weeks later, the patient presented multiple leptomeningeal and brain metastases spreading
14 from the sellar region. Regarding these observations, we conducted a systematic review of the literature in order
15 to investigate clinico-radiological features that should lead clinicians to suspect pituitary metastasis and how it
16 should impact the surgical management.

17

18 **Key words**

19 Pituitary; Metastasis; Leptomeningeal carcinomatosis; Melanoma; Transsphenoidal; Endoscopic surgery

20

21 **Résumé**

22 Nous rapportons un cas de mélanome malin révélé par une métastase hypophysaire. La tumeur a été
23 diagnostiquée à tort comme un adénome hypophysaire et une chirurgie transsphénoïdale agressive a été
24 compliquée par une fistule de liquide céphalorachidien. Neuf semaines plus tard, le patient a présenté plusieurs
25 métastases leptoméningées et cérébrales se propageant à partir de la région sellaie. Aux vues de ces constats
26 cliniques, nous avons conduit une revue systématique de la littérature afin de déterminer les caractéristiques
27 clinico-radiologiques qui devraient conduire les cliniciens à soupçonner une métastase hypophysaire et en quoi
28 cela doit impacter la gestion chirurgicale.

29

30 **Mots-clés**

31 Hypophyse; Métastase; Dissémination leptoméningée; Mélanome; Transsphénoïdal, Chirurgie endoscopique

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41 **Text**

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43 **Introduction:**

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45 The pituitary gland is an unusual location for metastases, accounting for around 0.4% of all intracranial
46 metastatic tumors [1] and representing less than 1% of surgically treated pituitary tumors [2]. Among
47 histologically-proven cases, breast and lung cancers are the most common cancers disseminating to the pituitary
48 gland [1,3], followed by prostate [4] and kidney cancers [1,5]. Pituitary metastases may reveal an unknown
49 cancer in 40% of cases [3], leading to subsequent delay in diagnosis and therapeutic management. Here we
50 report a rare case of pituitary metastasis of malignant melanoma misdiagnosed as a pituitary adenoma.
51 Aggressive surgical treatment was complicated by a breach of the arachnoid membranes, then leading to an
52 intracranial diffusion of the disease. Regarding these observations, we performed a systematic review of the
53 literature in order to investigate clinicoradiological features that should lead clinicians to suspect pituitary
54 metastasis and how it should impact the surgical management.

55

56 **Case description:**

57

58 *Initial presentation*

59 A 51-year-old woman without previous medical history, was admitted in our medical center for a rapid visual
60 disturbance. These symptoms began few months ago and were associated with a general fatigue. The
61 ophthalmological examination revealed a bitemporal hemianopsia. Endocrinological analysis showed modest
62 hyperprolactinemia (908 uUI/mL, normal range: 102-496 uUI/mL), hypocortisolism and hypothyroidism.
63 Computed tomography (CT) scans and brain magnetic resonance imaging (MRI) revealed a sellar lesion with
64 suprasellar expansion leading to a compression of the optic chiasm. The lesion had heterogeneous high signal
65 intensity on T1-weighted images, mild homogeneous enhancement on T1-weighted images with gadolinium
66 infusion and had low signal intensity on T2-weighted images (Figure 1A). There were no other brain
67 abnormalities on these exams. The patient underwent an exploration through a transsphenoidal endoscopic
68 approach to release optic chiasm compression. Intraoperatively, the tumor was gray-colored with a necrotic

69 component. There was no adjacent bone or dura invasion. A breach of the arachnoid membranes was observed
70 and sealed with fibrin-coated collagen fleece. Postoperatively, the patient recovered from her bitemporal
71 hemianopsia but developed a diabetes insipidus. Hydrocortisone, levothyroxine and desmopressin oral
72 substitution were required to balance endocrinological impairments in the early postoperative course.

73

74 *Histological examination*

75 The histological examination revealed a malignant tumor with melanotic pigmentation and necrosis (Figure 2).
76 The immunohistochemistry testing was positive for HMB45, Sox10 and MelanA proteins. The diagnosis was
77 consistent with a pituitary metastasis of malignant melanoma. BRAF mutation was positive, while cKIT and
78 NRAS mutations were negative.

79

80 *Postsurgical cerebrospinal fluid fistula*

81 The patient came back to the hospital 14 days after surgery with severe headache, drowsiness and signs of
82 intracranial hypotension. The CT scan showed disseminate pneumocephalus (Figure 1B). An endonasal
83 revision surgery was performed to seal the CSF fistula with an autologous fat graft.

84

85 *Oncological management*

86 The patient underwent a full-body skin exam and a full-body CT/PET scan: no primitive or other secondary
87 lesions were found. A new brain MRI was performed 9 weeks after surgery. It revealed contiguous extensions of
88 the pituitary metastasis to the frontal lobes. Other brain metastases were observed in the right frontal lobe and in
89 the right cingulate lobe (Figure 1C). In addition, the residual sellar tumor volume significantly increased in
90 comparison to the immediate postsurgical CT scan.

91 A combined targeted therapy with dabrafenib (anti-BRAF) and trametinib (anti-MEK) was then started for 3
92 months. Due to a rapid clinical deterioration and progression of the disease, the treatment was changed to a
93 monotherapy with vemurafenib (anti-BRAF) for 3 weeks. This treatment was stopped due to severe bilateral
94 uveitis and skin rash. A third-line treatment with pembrolizumab (anti-PD1 immunotherapy) was then
95 introduced. This therapy was stopped after the second infusion due to panhypopituitarism, that could be related
96 either to the tumor progression or to an immunotherapy-related hypophysitis.[6] The patient finally deceased 12
97 months after the initial surgery due to a diffuse progression of brain metastases, repeated seizures and
98 intracranial hypertension.

99

100 Systematic review of the literature:

101 A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews
102 and Meta-analyses (PRISMA) statement [7].

103 A literature search was performed in MEDLINE and Cochrane Library on May 5, 2020. The search strategy
104 used for MEDLINE was ((Pituitary OR Sella OR Sellar OR Hypophysis OR Neurohypophysis OR
105 Adenohypophysis) AND Metastas*) OR ("Pituitary Neoplasms/secondary"[Mesh]). Only symptomatic and
106 histologically confirmed cases were eligible. All cases of metastasis to the pituitary were initially screened.
107 Then, non-melanoma metastases to the pituitary and pituitary carcinomas were excluded from analysis. The
108 PRISMA flow diagram is provided in Figure 3. Thirteen studies were selected, including 15 cases of melanoma
109 metastases to the pituitary. These results are presented in Table 1.

110 Overall, the mean age was 58.3+/-16.3 years. There were only 3 females (20.0%). Ten patients (66.7%) had
111 visual disturbances, 2 patients (13.3%) had ophthalmoplegia, 3 patients (20.0%) had diabetes insipidus and 10
112 (66.7%) patients had anterior pituitary deficiency. One patient presented with an apoplexy syndrome.

113

114 Discussion:

115

116 Pituitary metastases have been described in autopsy series, but they remain rare in clinical condition. Among
117 them, few cases require a neurosurgical approach [8,9] with only 2.5 to 18.2% of pituitary metastases being
118 symptomatic [10]. In 40% of cases, pituitary metastases are the revealing condition of an underlying cancer [3].
119 Patients without previous neoplasm do not share the same clinical presentation as pituitary adenomas, with a
120 very high prevalence of ophthalmoplegia, visual field defects, visual acuity disorders and diabetes insipidus. By
121 contrast, posterior pituitary dysfunction and cranial nerve palsy is rarely reported in patients with pituitary
122 adenomas, excepted in case of apoplexy [11]. In addition, anterior pituitary gland dysfunction is observed in
123 most patient, with a prevalence of ACTH deficiency up to 71% [12]. The combination of ophthalmoplegia,
124 diabetes insipidus and/or adenohypophyseal dysfunction, the rapid installation of these symptoms and the
125 presence of a lateral extension on neuroimaging must lead clinicians to suspect pituitary metastases [1,11].

126

127 The occurrence of pituitary metastasis of malignant melanoma is very rare, with less than 20 cases reported in
128 the literature. Among them, there are autopsy reports in patients with disseminated metastatic spread [13–18].

129 Fifteen cases of symptomatic and histologically confirmed pituitary metastases of malignant melanoma were
130 reported in the literature [19–31]. Among them, visual disturbance was the most common presentation (10
131 cases). A biological antehypophyseal insufficiency was also very common (10 cases) while diabetes insipidus
132 was reported in only 3 cases. In two cases, a cranial nerve palsy was describe [25,30] and in another case, the
133 disease was revealed by an apoplexy [21]. Most patients had a previous history of melanoma.

134

135 Rare cases of primary melanocytic tumors of the sellar region are reported in the literature [32,33]. Differential
136 diagnosis between these primary lesions arising from the meninges and skin melanoma metastases can be
137 challenging in case of negative whole-body imaging. Nevertheless, BRAF mutations seem to be absent or very
138 rare in primary melanocytic tumors, while it is a common mutation in metastases from skin melanoma.[34,35]

139

140 Distant frontal and cingulate metastases observed in the present case may be related to the systemic progression
141 of the disease, independently of the pituitary metastasis. No other case of metastatic spread after transsphenoidal
142 surgical approach in pituitary metastases was reported in the literature, but only mentions of a possible
143 leptomeningeal spread after a breach of the arachnoid membranes, which were mainly related to an
144 intraoperative breaching of the diaphragma sellae [36,37]. One case of cerebrospinal fluid dissemination was
145 described after a transsphenoidal surgery for a pituitary adenoma [38] and another case was about a growth
146 hormone-producing pituitary carcinoma with spinal metastases following multiple surgeries [39].
147 Leptomeningeal spread of pituitary adenoma has been widely reported in patients who underwent craniotomies
148 before the era of mini-invasive endoscopic transsphenoidal approach [40–42].

149

150 There is no standardized treatment for pituitary metastases, and different approaches have been described,
151 including surgical resection, radiosurgery, radiotherapy and chemotherapy. While surgery is indicated for a
152 symptomatic purpose (including optic chiasm decompression in case of bitemporal hemianopsia) and
153 histopathological confirmation, it does not impact survival results [3,43]. Regarding our observations, it seems
154 crucial to prevent any breach of the arachnoid layer in order to avoid subsequent intracranial diffusion of the
155 disease. A gross total resection should not be attempted in case of doubtful clinicoradiological presentation
156 (including a rapid progression of symptoms, and/or an unusual combination of endocrine deficits, visual deficits
157 and cranial nerve palsy) or unusual intraoperative findings (including unattended bleeding or unusual aspect of
158 the tumor).

159

160 Conclusion:

161 We report a case of pituitary metastasis of malignant melanoma misdiagnosed as a pituitary adenoma.

162 Aggressive surgical treatment was complicated by a breach of the arachnoid membranes, then leading to an

163 intracranial diffusion of the tumor. As surgery does not impact survival in pituitary metastases, we suggest that

164 gross total resection should not be attempted in case of doubtful clinicoradiological presentation (including a

165 rapid progression of symptoms, and/or an unusual combination of endocrine deficits, visual deficits and cranial

166 nerve palsy) or unusual intraoperative findings. Indeed, a precautionous conservation of the arachnoid membranes

167 is necessary to avoid local or distant brain metastatic diffusion.

168

169 **Tables**

170

171 **Table 1:** Symptomatic Pituitary Metastases of Malignant Melanoma: Systematic Review of the Literature

172

173 **Images and legends**

174

175 **Figure 1:** (A) Preoperative Magnetic Resonance Imaging. From left to right: coronal T2 -weighted image,
176 coronal T1-weighted image without and with Gadolinium infusion and Sagittal T1-weighted image with
177 Gadolinium infusion. (B) Postoperative CT scan (12 days after surgery) showing diffuse pneumocephalus. (C)
178 Postoperative MRI (9 weeks from the surgery). From left to right: coronal T1-weighted images with Gadolinium
179 infusion and axial T1-weighted images with Gadolinium infusion. a: suprasellar enhancement; b and e: right
180 cingulate enhancement; c: bilateral basifrontal enhancements; d: right frontal enhancement.

181

182 **Figure 2:** Postoperative pathological studies. (A) Hematoxylin and eosin-stained section. Immunohistochemical
183 specimens show positive staining for HMB45 (B), Sox10 (C) and BRAF (D).

184

185 **Figure 3:** PRISMA flow diagram.

186

187 **Patient consent**

188 The patient has consented to the submission of this case report.

189

190 **Compliance with ethical standards**

191 Conflict of interest. The authors declare that they have no conflict of interest.

192

193

194

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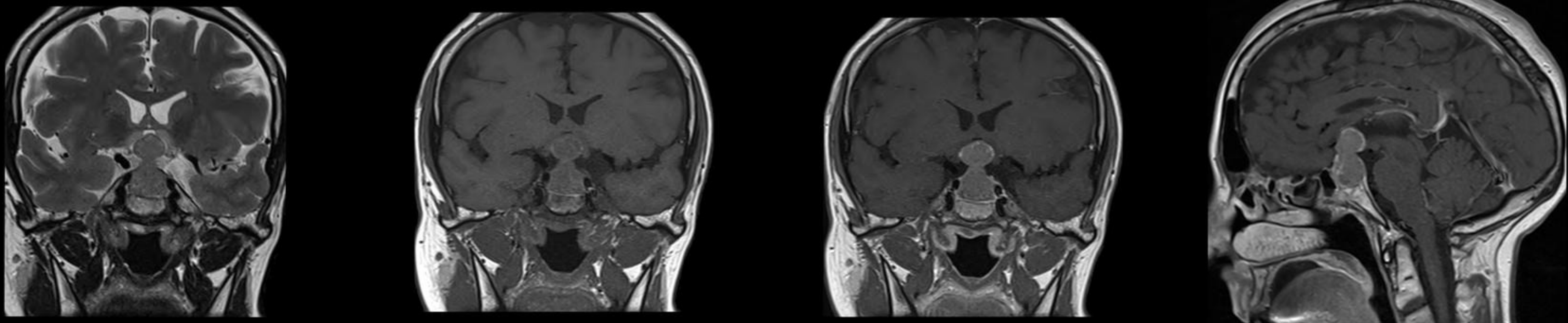
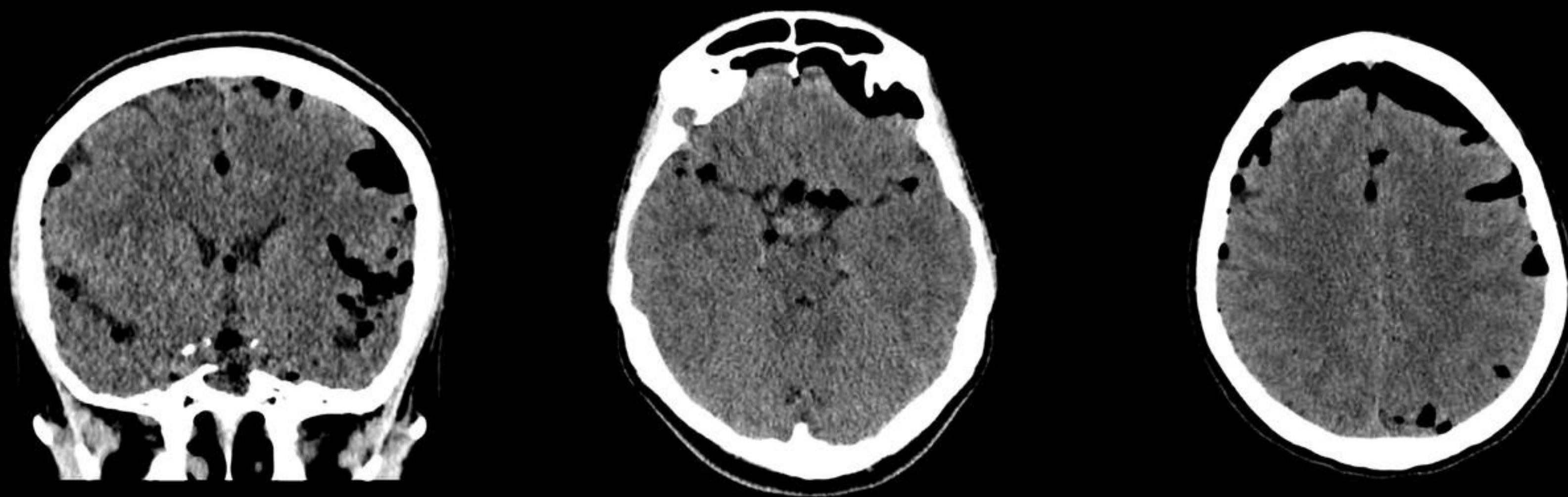
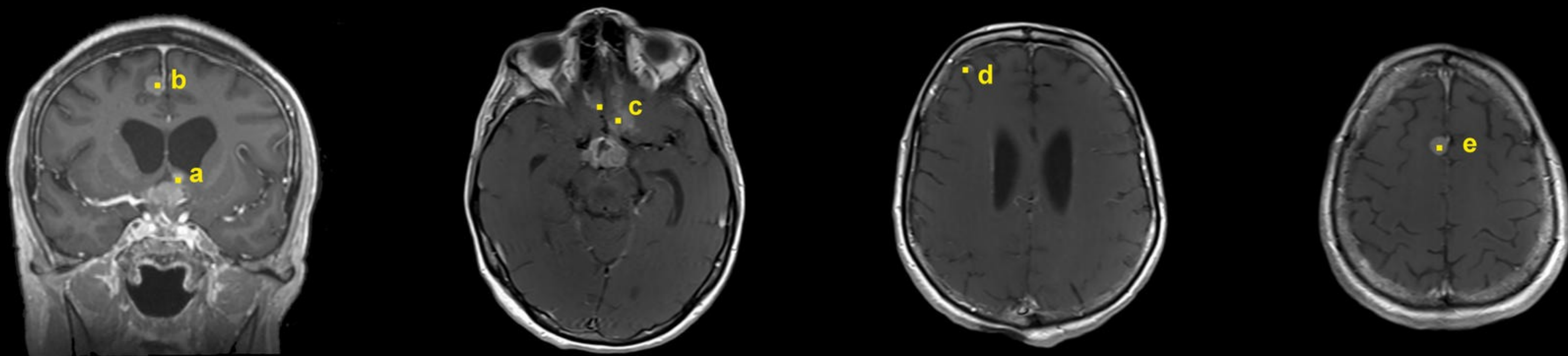
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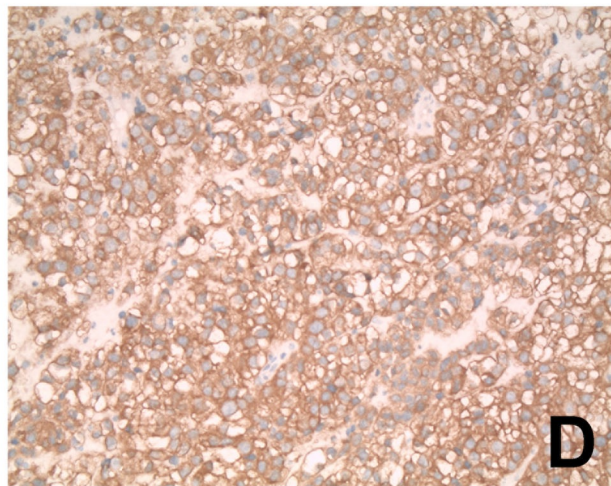
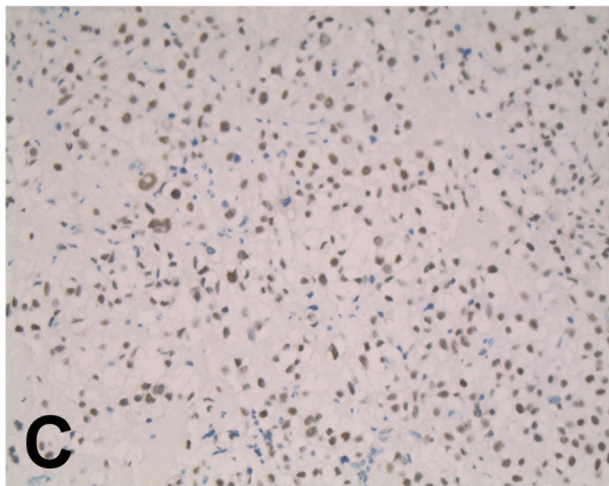
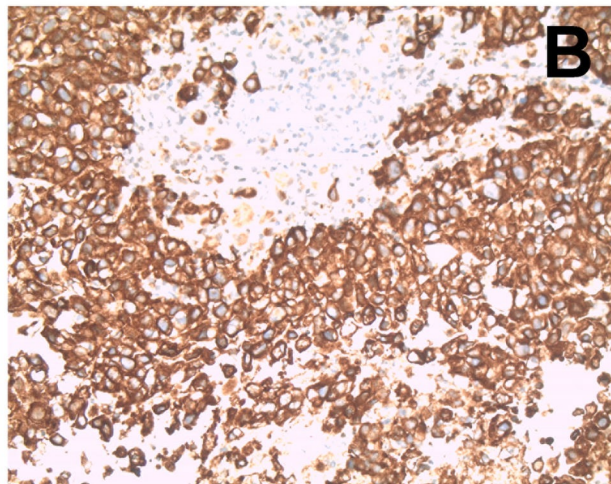
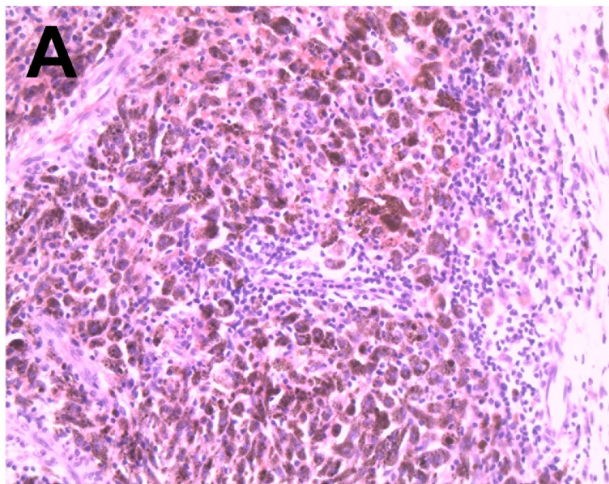
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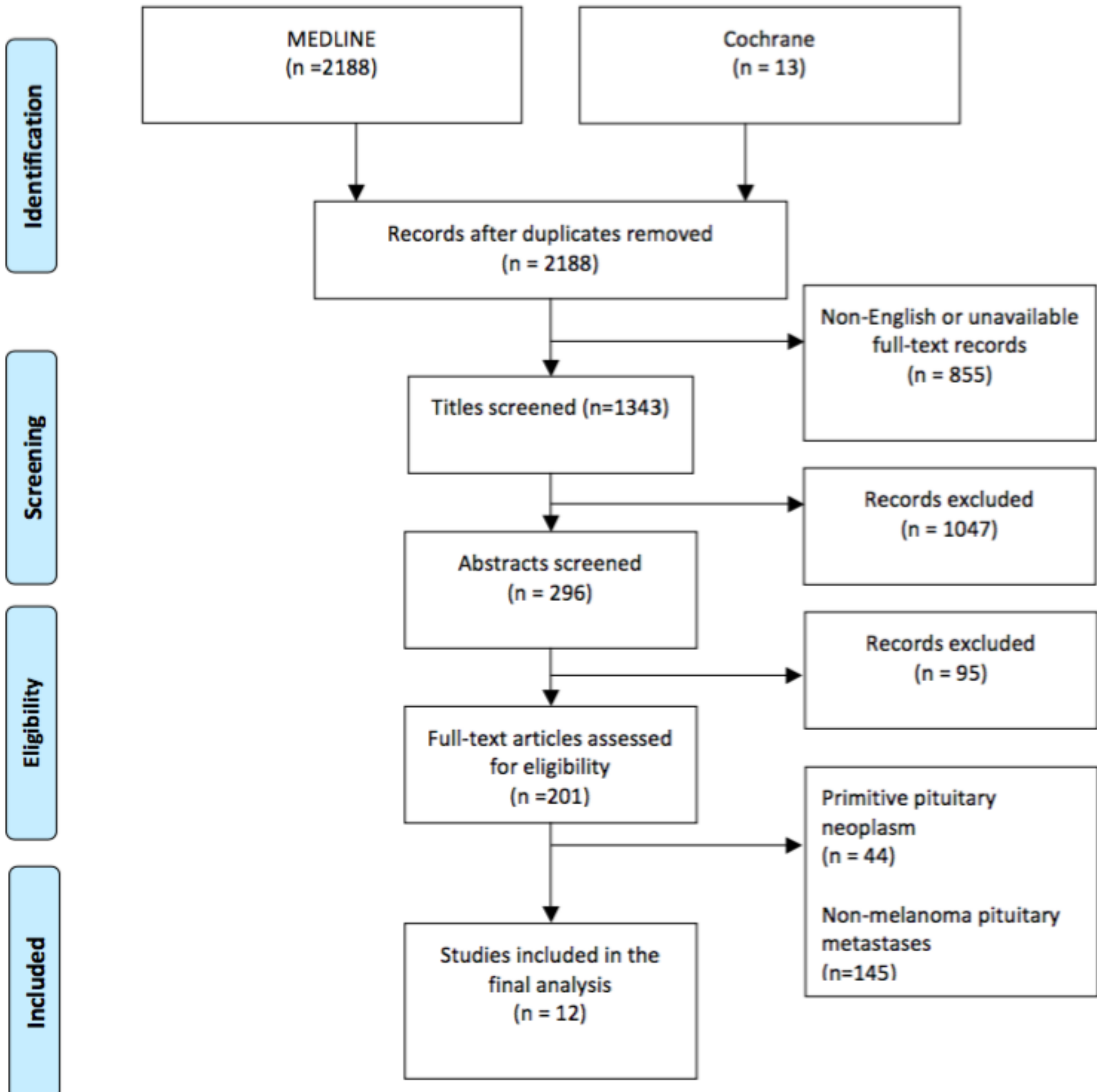


Table 1: Symptomatic Pituitary Metastases of Malignant Melanoma: Systematic Review of the literature

Case No	Authors & Year	Age (years), gender	Clinical presentation	Pituitary dysfunction	MRI findings Anterior / posterior lobe / sellar invasion	Histopathology and Immunocytochemistry	Melanoma Past history	Concomitant metastases or primary tumor at diagnosis	Treatment	Last follow-up
1	Mayr et al, 1993 (33)	25, male	Anterior pituitary dysfunction	Unknown	Sellar and suprasellar High T1, Low T2 signal Gadolinium enhancement	Details not provided	Unknown	Presence of systemic metastases and brain metastases	Details not provided	unknown
2	Leung et al, 2003 (8)	46, male	Diabetes insipidus Erectile dysfunction	Diabetes insipidus Decreased Testosterone, FSH, LH Decreased FT4 Decreased ACTH	Sellar Heterogeneous high T1 signal Low T2 signal Heterogeneous Gadolinium enhancement	Melanin pigmentation S-100 HMB-45	Right ear lobe melanoma. Clark IV. Lymphadenopathy. 5 years ago.	Negative whole-body FDG-PET	Transsphenoidal resection. Whole-brain irradiation.	7 months
3	Jung et al, 2007 (26)	70, male	Visual disturbance	Increased PRL Decreased ACTH Decreased FT4, FT3	Sellar and suprasellar Iso T1, High T2 signal Gadolinium enhancement	Melanin pigmentation S-100 HMB-45	Left big toe melanoma, T3N1M0, 15 months ago	Mediastinal, liver, inguinal and kidney lesions	Transsphenoidal resection. No adjuvant therapies	1 month. Death
4	McCutcheon et al, 2007 (27)	77, male	Ptosis and diplopia Visual disturbance	Decreased GH	Sellar, suprasellar, upper clivus extension	S-100 HMB-45	Anterior chest wall, Clark IV. Lymphadenopathy. 33 months ago.	Negative exploration	Transsphenoidal debulking. Radiotherapy.	6 months
5	McCutcheon et al, 2007	42, male	Diabetes insipidus Visual disturbance	Diabetes insipidus, Decreased GH Decreased FT4,3 Decreased ACTH	Sellar and suprasellar	Melanin pigmentation HMB-45	Anterior chest wall, Clark IV. 77 months ago.	Subcutaneous chest nodules Cervical, lung and retroperitoneal lymphadenopathy	Transsphenoidal debulking. Whole-brain irradiation (30 Gy). Thalidomide and temozolomide.	4 months Death
6	Guzel et al, 2009 (9)	46, female	Headache	No abnormalities	Sellar Iso T1, Iso T2 signal Gadolinium enhancement	S-100 HMB-45	Left shoulder melanoma 7 years ago. Lymphadenopathy 1 year ago.	Right pontocerebellar angle lesion	Stereotactic Biopsy. Whole-brain irradiation. Temozolomide	9 months Death
7	Kano et al, 2009	47, male	Diabetes insipidus	Diabetes insipidus.	unknown	Details not provided	Unknown	Unknown	Surgery. Stereotactic radiosurgery	34.8 months Death
8	Kano et al, 2009 (32)	52, female	Ophthalmoplegia	No pituitary dysfunction	unknown	Details not provided	Unknown	Unknown	Stereotactic radiosurgery	21.8 months Death
9	Wang et al, 2011 (14)	78, male	Visual disturbance, weight loss	Decreased Testosterone Decreased FT4, FT3 Decreased ACTH	Sellar and suprasellar High T1, low T2 signal Mild Gadolinium enhancement	Melanin pigmentation	-	Left frontal lobe lesion Liver and splenic lesions	Transsphenoidal debulking	1 week Death
10	Masui et al, 2013 (10)	68, male	Sudden headache and visual disturbance. Apoplexy	Decreased FT4, FT3	Sellar and suprasellar High T1, Low T2 signal, Heterogenous Gadolinium enhancement	Necrosis S-100 HMB-45	-	Stomach primary melanoma	Transsphenoidal debulking. No adjuvant therapies.	2 months
11	Zoli et al, 2013 (28)	unknown	Visual disturbance	unknown	unknown	unknown	unknown	unknown	Transsphenoidal resection	unknown
12	Burkhardt et al 2015	73, male	Visual disturbance, Anterior pituitary dysfunction, Diabetes insipidus	unknown	unknown	Details not provided	Unknown	Unknown	Surgery. Stereotactic radiotherapy (39Gy)	unknown
13	Yang et al, 2017 (11)	62, female	Visual disturbance	Increased PRL Decreased FT4, FT3	Sellar and suprasellar Iso T1, Iso T2 signal, Homogeneous Gadolinium enhancement, Bone destruction	Melanin pigmentation No necrosis S-100 HMB45	Left heel melanoma diagnosed 2 years ago. Stage III	Portal and retroperitoneal lymphadenopathy, Liver lesions	Transsphenoidal debulking. No adjuvant therapies.	22 months
14	Goulart et al, 2017 (29)	52, male	Visual disturbance	Panhypopituitarism	Suprasellar Gadolinium enhancement	Details not provided	Unknown	Unknown	Transsphenoidal debulking. No adjuvant therapies.	5 months
15	Castle-Kirszbaum et al, 2018 (30)	78, male	Visual disturbance	Increased ACTH Decreased FT4, FT3	Sellar and suprasellar High T1, Low T2 signal Gadolinium enhancement	Details not provided	Unknown	Disseminated lesions	Transsphenoidal debulking. No adjuvant therapies (palliation)	unknown-