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Comprehensive Evaluation of Rare Pituitary Lesions: A Single Tertiary Care Pituitary Center Experience and Review of the Literature

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Abstract
The 2017 World Health Organization classification of central nervous system and endocrine tumors have introduced significant changes in the diagnostic criteria for pituitary lesions. The aim of our paper is to describe the epidemiological, clinico-pathological, and radiological features of a single consecutive institutional surgical series of rare pituitary lesions, using these new criteria. Of the 316 endoscopic endonasal trans-sphenoidal approaches performed for pituitary lesions between 2010 and 2018, 15 rare lesions were encountered. These included metastases, pituitary carcinomas, pituicytomas, granular cell tumor, primary pituitary lymphomas, germinoma, mixed gangliocytoma–adenoma, hypophysitis, and pituitary hyperplasia. Their clinical, radiological, and pathological features are herewith presented along with a literature review that enabled us to propose an algorithm to facilitate a diagnosis for rare pituitary lesions.

Keywords Pituitary lesion · Rare disease · Surgery · Pathology · Radiology

Introduction

Tumors of the sellar region represent around 10–15% of all intracranial neoplasms and include both pituitary and non-pituitary diseases [1]. In addition to pituitary adenomas, which represent about 90% of cases [2], a wide range of other rare non-neuroendocrine lesions can be observed.

Pituitary tumors are currently classified using the criteria recently published in the World Health Organization (WHO) classification of central nervous system (CNS) [3] and endocrine tumors [1]. It is worth noting that the evolution of the terminology from the traditional term "pituitary adenoma" to "pituitary neuroendocrine neoplasm (PitNEN)" has recently been proposed to better define the variable clinical spectrum of these tumors that can behave differently despite similar morphological features [4].

Since individual clinical and radiological characteristics of non-neuroendocrine sellar lesions are lacking, they are frequently not distinguishable from classic PitNENs based on clinical and imaging data alone and represent a challenge for both clinicians and radiologists. Consequently, the differential diagnosis mostly relies on both intraoperative findings of experienced surgeons and careful pathological analysis.

The aim of our paper is to describe the epidemiological, clinico-pathological, and radiological features of our surgical series of rare non-adenomatous pituitary lesions, integrating our experience with the most recent data from the literature.

Materials and Methods

Clinico-pathological findings of a consecutive series of pituitary lesions resected at the Neurosurgical Department of the University Hospital of Lausanne between January 2010 and September 2018 were retrospectively reviewed. Only adult patients (> 18 years) were included in the analysis. A classical endonasal endoscopic transsphenoidal approach [5] was used in all cases, with a trans-tuberculum approach for lesions with a suprasellar extension [6]. The surgical outcome was evaluated as gross total resection (GTR, defined as no residual

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Table 1 The antibodies used to perform the immunohistochemical analysis are here listed in details

Antibodies	P/M (clone)	Source
Synaptophysin	M (SP11)	Ventana, Tucson, AZ, USA
Chromogranin A	M (LK2H10)	Ventana
GH	M (S4-9-2A2)	BioGenex Laboratories, San Ramon, CA, USA
FSH	M (FSH03)	Neomarkers, Westinghouse, CA, USA
LH	M (3LH586YHG)	BioGenex
TSH	M (TSH01 + TSH02)	Neomarkers
Prolactin	P	Ventana
ACTH	M (02A3)	Dako, Carpinteria, CA, USA
αhCG	P	Ventana
TTF1	M (8G7G3/1)	Dako
CD117	P	Dako
CD20	M (L26)	Novocastra, Newcastle, UK
CD3	M (F2.38)	Ventana
IgG	P	Dako
IgG4	M (HP6025)	Thermo Scientific, Rockford, IL, USA
GFAP	M (6F2)	Dako
MAP2	M (BK-T.1)	Chemicon International, Temecula, CA, USA
S100	P	Novocastra
p53	M (D07)	Dako
Cytokeratin	M (AE1/AE3)	Dako
Ki67	M (MIB1)	Dako

P polyclonal, *M* monoclonal

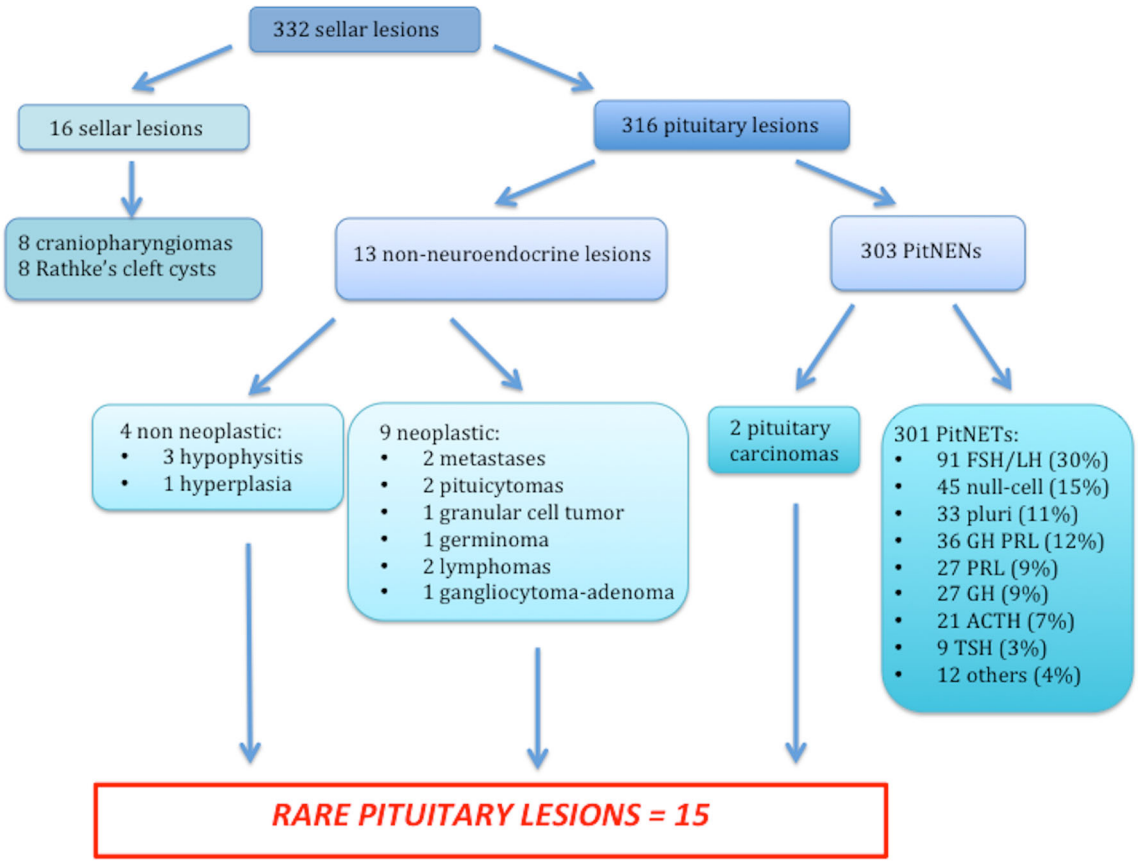

Fig. 1 Summary of the surgical series of sellar lesions operated between January 2010 and September 2018. Among 316 pituitary lesions, 15 rare lesions were identified (4.7%) and included 2 pituitary carcinomas (13%), 9 non-neuroendocrine neoplasms (60%), and 4 non-neoplastic lesions (27%). PitNENs, pituitary neuroendocrine neoplasms; PitNETs, pituitary neuroendocrine tumors; pluri, plurihormonal pituitary tumors

Table 2 The clinico-radiological features of patients with rare pituitary lesions, as well as the outcomes after treatement, are here detailedThe clinico-radiological features of patients with rare pituitary lesions, as well as the outcomes after treatement, are here detailed

Number	Pathology	Age at surgery (years)	Sex	Complete pituitary insufficiency	Partial pituitary insufficiency	Diabetes insipidus	Visual symptoms	Suprasellar extension	Hydrocephalus
1	PRL carcinoma	70	F	Y	–	N	N	Y	N
2	PRL carcinoma	40	M	N	Y (LH FSH)	N	Y	Y	N
3	Pituitary meta	65	M	Y	–	N	N	N	N
4	Pituitary meta	54	F	N	N	Y	N	Y	N
5	PIT	21	M	N	N	N	Y	Y	N
6	PIT	69	M	Y (apoplexy)	–	N	Y (apoplexy)	Y	N
7	GCT	83	F	Y	–	N	Y	Y	N
8	PPL	74	M	N	N	N	Y	N	N
9	PPL	74	M	N	Y (TH)	N	Y	N	N
10	Ganglio + GH	48	F	N	N	N	N	N	N
11	Germinoma	38	F	Y	–	Y	Y	Y	N
12	IgG4 Hypophysitis	20	F	N	N	N	Y	Y	N
13	IgG4 Hypophysitis	69	F	Y	–	Y	N	Y	N
14	Granulomatous hyophysitis	35	F	N	N (stalk effect)	N	N	Y	N
15	Hyperplasia	70	F	N	N	N	N	N	N

Number	Cavernous sinus extension	Sphenoid sinus extension	Surgical result	Visual outcome	Endocrine outcome	FU (months)	Adjuvant TT	Result
1	Y	Y	STR	–	Complete pituitary insufficiency DI	38	DA + RTH + surgery + CHT	Death (cranio-cerebral dissemination)
2	Y	Y	STR	W	Complete pituitary insufficiency	45	RTH + CHT	Stability (frontal metastasis)
3	Y	N	Biopsy	W	Complete pituitary insufficiency Transient DI	7	RTH	Death
4	Y	N	Biopsy	–	Complete pituitary insufficiency DI	2	RTH adjuvant	Death
5	Y	N	STR	B	Complete pituitary insufficiency DI	18	N	Remission
6	Y	N	GTR	Stable	Complete pituitary insufficiency	24	N	Cured
7	Y	N	GTR	Stable	Complete pituitary insufficiency	36	N	Cured
8	Y	N	Biopsy	Stable	Cortico insufficiency Transient DI	36	RTH + CHT	Remission

Table 2 (continued)

9	Y	N	Biopsy	B	No deficit	52	CHT	Remission	
10	Y	N	GTR	–	No deficit	54	N	Cured	
11	N	N	STR	Stable	Complete pituitary insufficiency DI	–	–	–	
12	N	N	GTR	B	No deficit	9	N	Cured	
13	N	N	GTR	–	Complete pituitary insufficiency DI	24	N	Cured	
14	N	N	Biopsy	–	No deficit	1	N	Cured	
15	N	N	GTR	–	No deficit	–	–	–	

ACTH adrenocorticotropic hormone, *B* better, *CHT* chemotherapy, *CPH* craniopharyngioma, *Cortico* hypothalamic–pituitary–adrenal axis, *DI* diabetes insipidus, *F* female, *Ganglio* gangliocytoma, *GCT* granular cell tumor, *GTR* gross total resection, *M* male, *Meta* metastasis, *N* no, *PIT* pituicytoma, *PPL* primary pituitary lymphoma, *RCC* Rathke's cleft cyst, *RTH* radiotherapy, *STR* subtotal resection, *TH* thyroid hormone, *Thyro* thyrotrophic axis, *W* worse, *Y* yes

tumor visible at the postoperative MRI), subtotal resection (STR, with a resection > 80%), and biopsy.

All tissues were fixed in buffered formalin (formaldehyde 4% wt/vol and acetate buffer 0.05 M) and routinely processed to paraffin. All cases were stained with hematoxylin–eosin for the morphologic evaluations. Representative sections were selected for immunohistochemical stains performed using the Ventana Benchmark XT autostainer (Ventana Medical System, Tucson, AZ, USA) including the antibodies listed in Table 1.

We performed a literature search for each rare non-adenomatous pituitary lesion identified in our series to better define the clinical, radiological and pathological features, and outcomes.

Results

Based on our series of 316 pituitary lesions, 301 were PitNETs and 15 (4.7%) included two metastases, two pituitary carcinomas, two pituicytomas, one granular cell tumor, two primary pituitary lymphomas (PPL), one germinoma, one mixed gangliocytoma-adenoma, three hypophysitis, and one pituitary hyperplasia (Fig. 1).

The series included six men (40%) and the mean age of our cohort of patients was 55 years. The most important clinical and radiological characteristics are reported in Table 2.

The most common clinical presentation was headache, followed by visual loss and hypopituitarism. Following surgery, visual deficits improved in three patients (one pituicytoma, one PPL, and one hypophysitis), remained stable in four patients (one pituicytoma, the GCT, one PPL, and the germinoma), and worsened in two patients (one pituitary metastasis and one carcinoma) secondary to disease progression. Postoperatively, two patients (13%) developed panhypopituitarism (one carcinoma and one pituitary metastasis), one patient (7%) developed hypopituitarism and diabetes insipidus (one pituicytoma), one patient (7%) developed diabetes insipidus (one carcinoma), and one patient (7%) presented isolated corticotroph insufficiency (one PPL). GTR was obtained in six cases (40%): one pituicytoma, the granular cell tumor, the mixed gangliocytoma–adenoma, the pituitary hyperplasia, and two hypophysitis. STR was performed in four cases (27%): both pituitary carcinomas, one pituicytoma, and the germinoma. In five cases, a biopsy was performed (33%): both pituitary metastases, both PPL, and one hypophysitis.

Of our two pituitary carcinomas, one presented a lumbar extramedullary metastasis and the Ki67 index increased from 3% in the pituitary "adenomatous tissue" to 20% in carcinomatous tissue. p53 marked 10% of cells in these specimens. The time between the first intervention and the diagnosis of carcinoma was of 134 months. The other case presented a frontal metastasis. The Ki67 proliferative index changed from

< 1% with no cellular atypical characteristics and a negative immunohistochemistry analysis in the initial resected PitNET to a Ki67 of 10% and a high expression of p53 in the carcinoma operated 122 months after.

In our series, pituitary metastases were secondary to breast carcinoma and lung adenocarcinoma. Patients presented with diabetes insipidus (one case) and pan-hypopituitarism with eyelid ptosis secondary to cavernous sinus invasion (one case). The pituitary metastases progressed during follow-up and patients died at 2 and 7 months from surgery, respectively.

The mixed gangliocytoma–adenoma and the granular cell tumor were in remission at 54 and 36 months of follow-up, as well as the two pituicytomas, which were free of disease after 18 and 24 months. The patient with the germinoma was lost at follow-up. The two PPLs were in remission after surgery combined with adjuvant treatment at 36 and 52 months of follow-up, respectively.

No recurrences were detected in patients with hypophysitis (two cases of IgG4-related hypophysitis and one case of granulomatous hypophysitis).

Discussion

Among rare pituitary diseases, pituitary carcinomas, non–neuroendocrine neoplasms, and hypophysitis represent a challenge for clinicians and radiologists because their clinico-radiological features are non-specific. Differentiating between them and with the more frequent PitNETs is crucial for the therapeutic approach and prognosis. These pathologies represented 4.7% of 316 pituitary lesions operated in our center over 8 years. In the present study, we analyzed the important epidemiological and clinico-pathological features of this series of rare pituitary pathologies, integrating them with literature data, with an aim to better define the therapeutic approach.

Hormonal Hypersecretion

In addition to PitNETs, symptoms related to hormone hypersecretion can also be found in association with pituitary carcinoma and mixed gangliocytoma–adenoma.

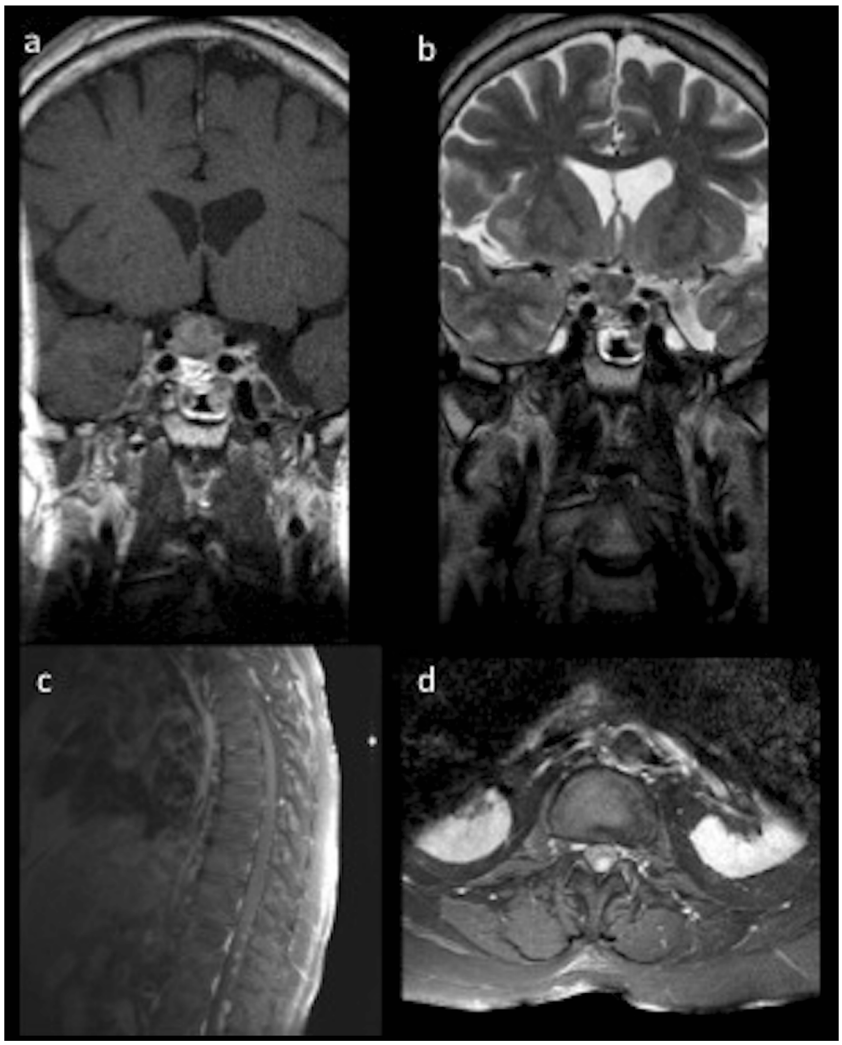

Fig. 2 T1-weighted (**a**) and T2-weighted (**b**) cerebral MRI in the coronal plane showing a sellar lesion with a suprasellar extension and a possible invasion of the cavernous sinus on the right side. The images are consistent with a pituitary adenoma. A medullary MRI (**c**, sagittal view and **d**, axial view) showed the presence of drop metastasis. The pathology was consistent with a PRL-secreting neoplasm and the presence of secondary localizations allowed the diagnosis of pituitary carcinoma (Fig. 5)

Table 3 The clinical, radiological and pathological features for each rare pituitary lesion are here summarized

	Pituitary carcinoma	Pituitary metastasis	Pituicytoma and GCT	Primary pituitary lymphoma	Gangliocytoma	Germinoma	Hypophysitis	Hyperplasia
Clinical features	> 50 y Mostly hypersecretory syndromes (> ACTH or PRL)	Oncologic history DI	50 y DI	50 y Immunosuppression CN palsy DI in 1/3 of patients	40–50 y Acromegaly or hyperPRL (mixed gangliocytoma/-adenoma)	> 10–20 y DI CSF analysis for AFP and Beta-hCG	Use of immunotherapy/-systemic granulomatous disease/IgG4-related disease	Pregnancy Primary hypothyroidism, hypogonadism hypocorticism Medication intake Visual disturbance rare
Radiological features	CNS or distant metastases	Thickening of the stalk Cavernous sinus invasion Bone erosion Absent posterior bright spot Strong CE Central necrosis Dumb-bell shape	Solid lesion Iso on T1w Hyper in T2w Pit: Strong CE Flow voids may be present No calcification GCT: Heterogeneous CE	Iso on T1w Hypo to iso on T2w CE heterogeneous Search for other cerebral localization	Solid lesion Hypo T1w and T2w Cysts and calcifications not frequent	Iso to hypo on T1w and T2w Strong CE and heterogeneous Cysts and calcifications in 1/3 of tumors Pituitary gland displaced Pineal and periventricular region also involved	Mild and symmetric gland enlargement Midline stalk thickening No posterior bright spot	Diffuse symmetrical pituitary enlargement CE homogeneous Normal pituitary not identifiable
Pathological features	Similar morphological and immunohistochemi-cal features of pituitary adenomas Ki67 > 3% p53 positive mitoses > 2/10 HPF	Depend on the primary neoplasm Immunophenotype depends on the primary neoplasm	Solid sheets of spindle cells Abundant granular eosinophilic cytoplasm in GCTs No atypia nor mitosis TTF-1 expression Ki67 low	B-cell lymphoma most commonly Immunophenotype depends on the lymphoma type	Large mature ganglion cells No mitosis Synaptophysin and NF, CgA and MAP-2+ PitNET frequently associated	Morphology and immunophenotype depend on the histotype	Lymphocytic infiltration in a normal gland (LH) Multinucleated giant cells in GH Infiltration of foamy histiocytes in XH IgG4-positive plasma cells infiltration in the IgG4-RH	Intact reticulin network Non-neoplastic polyclonal proliferation of a specific adenohypophyseal cell subtype

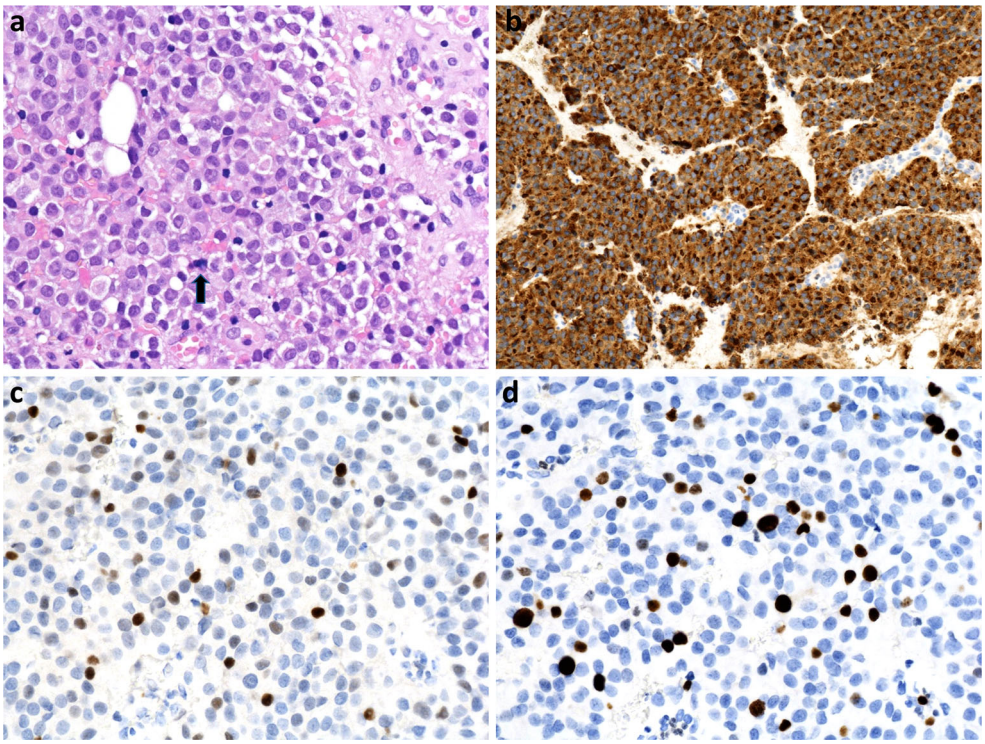

Fig. 3 Pituitary carcinoma shows hypercellularity and is composed of atypical cells. Mitotic activity (Ki67) is present (**a**). Tumor cells are positive for prolactin (**b**). Nuclear p53 immunoreactivity is observed in some cells (**c**) and the Ki67 proliferative index is 5% (**d**)

Pituitary carcinoma is traditionally defined as an anterior pituitary tumor showing craniospinal dissemination and/or systemic metastases [1, 3]. It represents less than 1% of anterior pituitary neoplasms with an annual incidence of about 0.1 cases per 100,000 population [1]. However, since metastases are often clinically occult at first diagnosis, their incidence may be underestimated. Like PitNETs, pituitary carcinomas can produce almost every type of pituitary hormone, although PRL or ACTH are the most frequent. About 20% of tumors are clinically non-functioning (silent) [7–9]. In our cohort, both cases were PRL-secreting carcinomas with clinically evident galactorrhea. Beside CNS or distant metastases, carcinomas do not show peculiar radiological features (Fig. 2). Pituitary carcinomas show overlapping morphological and immunohistochemical features observed in PitNETs, although hypercellularity, nuclear pleomorphism, increased mitotic activity, necrosis, high microvascular

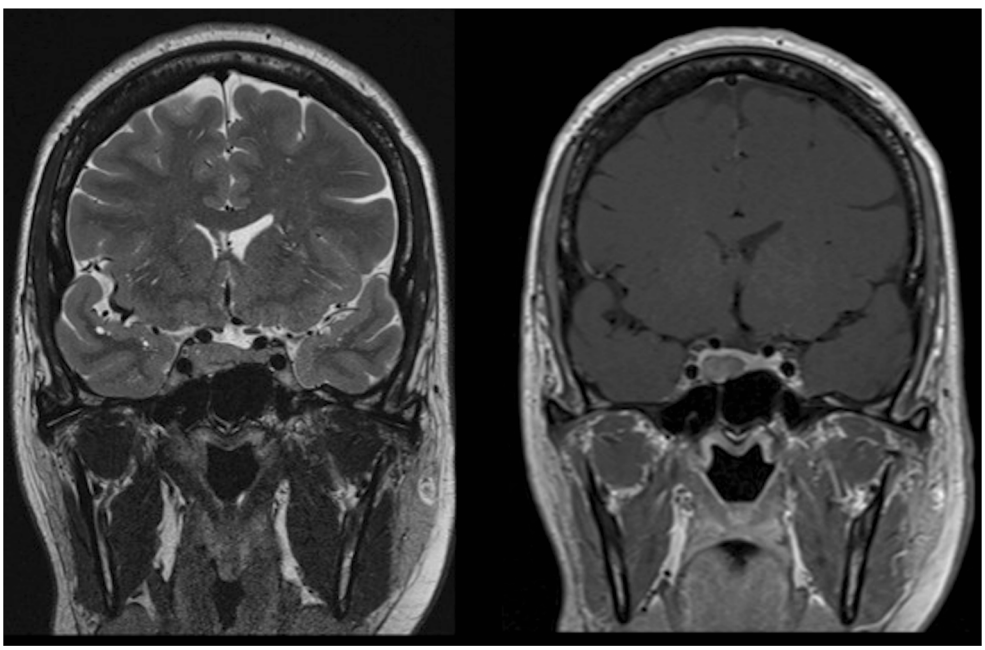

Fig. 4 Coronal views of a T2-weighted (left) and T1-weighted cerebral MRI after gadolinium administration (right). A sellar lesion with a parasellar extension on the right side is evident. The contrast enhancement was mild when compared to the normal pituitary, which was displaced towards the left side of the sella. Pathology showed a mixed pituitary gangliocytoma–adenoma

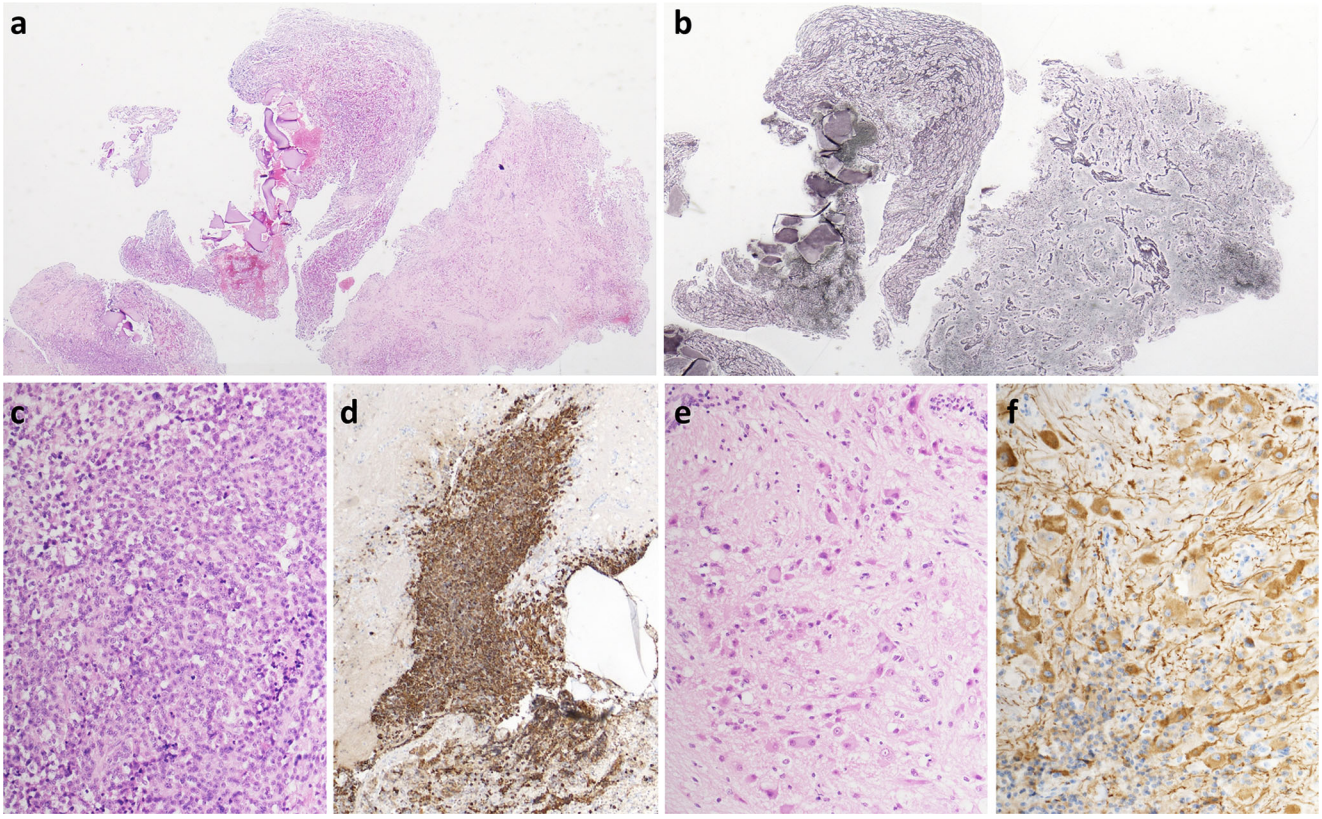

Fig. 5 Mixed pituitary gangliocytoma–adenoma. At lower power magnification (**a**), the neoplasms correspond to the right fragment, while the central fragment corresponds to a normal pituitary gland, as confirmed by reticulin stain (**b**). The tumor is composed of a somatotroph pituitary adenoma (**c**) positive for GH (**d**), while the gangliocytoma component, characterized by large mature ganglionic cells (**e**), is positive for MAP-2 (**f**)

density, high Ki67 proliferative index, p53 immunoreactivity, loss of p27 expression, and overproduction of HER2/Neu are more frequently observed in carcinomas (Table 3 and Fig. 3). However, they are not per se diagnostic markers of malignancy [10].

Gangliocytomas are neuro-epithelial indolent WHO grade I tumors composed of mature neoplastic ganglion cells. In the sellar region, they are usually associated with pituitary adenomas (mixed gangliocytoma–adenoma) [11]. Patients most often present endocrine symptoms such as acromegaly and symptoms of hyperprolactinemia [11]. Sellar gangliocytomas generally present as well-delimited solid masses in the sellar region, but in more than one third of cases they invade the cavernous sinus and/or the sphenoid sinus [11]. Their radiological features are summarized in Table 3 and Fig. 4. Gangliocytomas are composed of large mature ganglionic cells frequently binucleated with prominent nucleoli associated or not with an adenoma component [3]. Mitoses are absent. Cells stain positive for synaptophysin and neurofilament, chromogranin A, and MAP-2, but they are negative for GFAP (unless a glial tumoral component is also present). Most frequently, a mixed GH-PRL adenoma (43%) or GH adenoma (33%) may be associated with the gangliocytoma [11] (Fig. 5).

Diabetes Insipidus

Any pituitary lesion can be associated with hypopituitarism, usually secondary to mass effect. The presence of diabetes insipidus (DI), on the other hand, can suggest a germ cell tumor or a lesion involving the posterior pituitary (i.e., pituicytoma, metastases, PPL), when the diagnosis of craniopharyngioma is ruled out.

Germ cell tumors account for 0.15% of lesions in transsphenoidal series [12] and among them germinomas represent the more frequent tumor type followed by teratoma and mixed germ cell tumor [1, 13, 14]. Radiological features are summarized in Table 3 and Fig. 6. Germinomas are typically composed of large, uniform, polygonal cells with pale cytoplasm. Nuclei are centrally located, with dispersed chromatin and one or more prominent nucleoli. Tumor cells grow forming lobules and nests separated by a fibrovascular stroma in which a rich reactive lymphocytic infiltration is observed (Fig. 7). Rare scattered β-hCG positive syncytiotrophoblastic cells can be present. Tumor cells are strongly immunoreactive for CD117 (c-kit), SALL4, OCT-4, and PLAP and are negative for cytokeratins, CD30, α-fetoprotein, and SOX2. Despite their exquisite sensitivity to radiation, surgery still plays a pivotal role to get diagnostic tissue, for CSF collection and analysis,

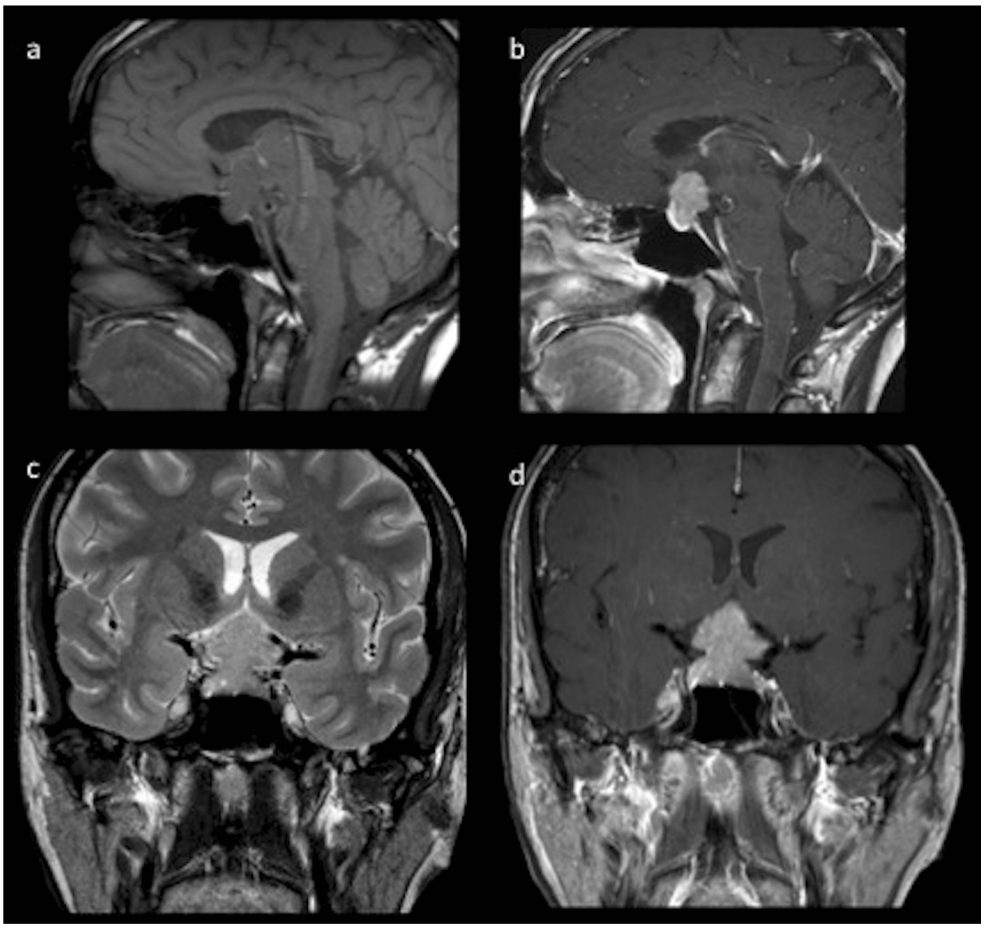

Fig. 6 Sagittal (**a** and **b**) and coronal view (**c** and **d**) of a sellar lesion with an important suprasellar extension with a flocculate profile. The contrast enhancement (**b** and **d**) is heterogeneous and milder when compared to the normal gland, which is displaced anteriorly. Pathology confirmed a germinoma (Fig. 7)

and for cytoreduction [15–17]. The surgical treatment depends on the exact localization of the tumor and on its lateral extension. Germinomas are strongly responsive to radiation therapy and chemotherapy with a long-term survival of 90% [15, 18].

Tumors of the posterior pituitary lobe are low-grade neoplasms representing a morphological spectrum of a single entity, believed to derive from pituicytes, the specialized glial cells of the posterior pituitary [19, 20]. An innovative aspect of the WHO classification is the identification of thyroid transcription factor-1 (TTF-1) expressing pituitary tumors, which represent a morphological spectrum of a single nosocomial entity including pituicytoma, spindle cell oncocytoma, granular cell tumors, and sellar ependymomas [1]. These are all considered low-grade non-neuroendocrine tumors [21]. Pituicytomas account for less than 0.1% of sellar tumors, spindle cell oncocytomas for about 0.4%, and granular cell tumors for about 0.5%. Only seven cases of sellar ependymoma have been reported [22].

The most common radiological features are summarized in Table 3 and Figs. 8 and 9. Pituicytomas are composed of solid

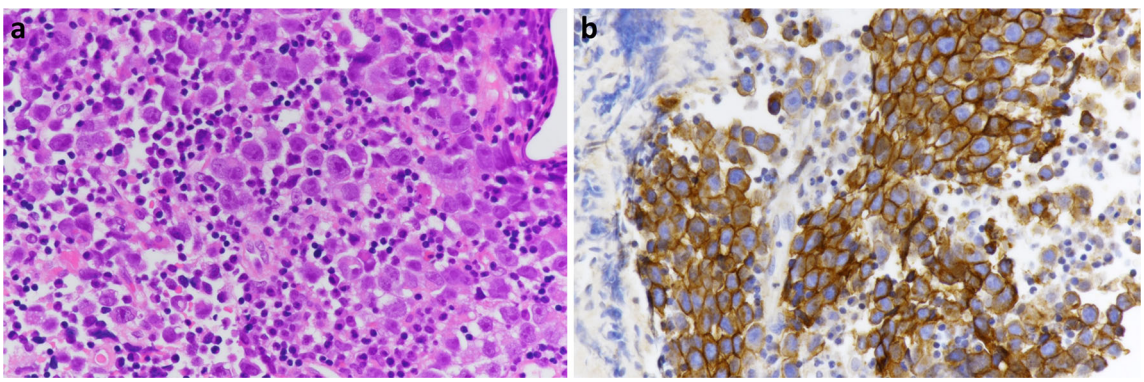

Fig. 7 Germinoma composed of large, uniform, polygonal cells. Nuclei are centrally located with dispersed chromatin and one or more prominent nucleolus (**a**). Tumor cells are strongly immunoreactive for CD117 (**b**)

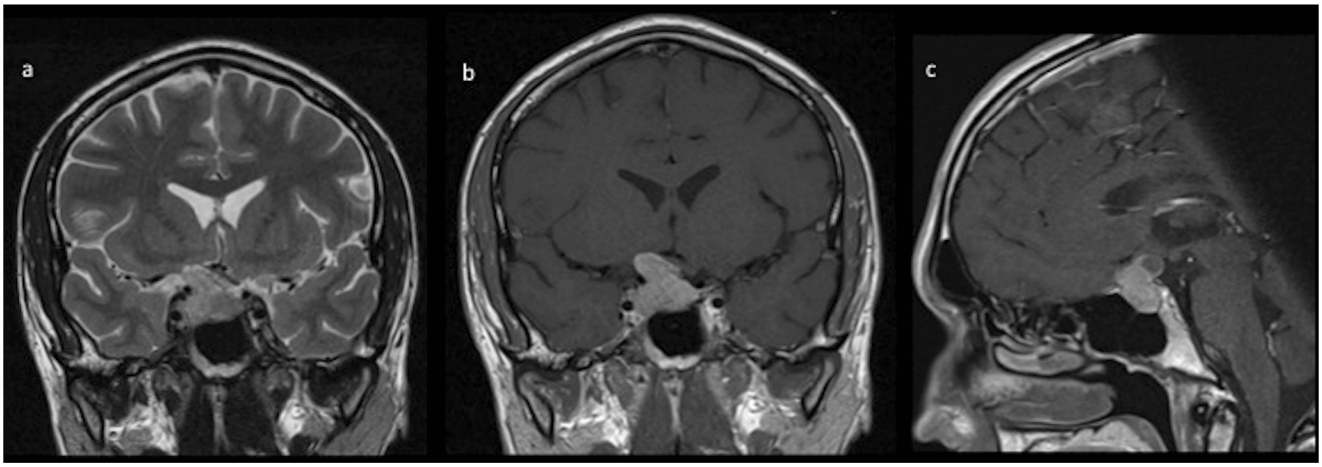

Fig. 8 Cerebral MRI showing a sellar lesion with a suprasellar extension. The T2-weighted (**a**) and T1-weighted coronal slices after gadolinium administration (**b**) show a suprasellar extension predominant on the right side with compression of the optic chiasm. A postero-superior cystic portion is visible in the T1-weighted sagittal MRI (**c**). The contrast enhancement is important and the bright spot corresponding to the posterior pituitary lobe was not visible. Pathology confirmed a pituicytoma

sheets of spindle cells forming fascicles or a storiform pattern. The tumor cell cytoplasm is eosinophilic with well-defined cell borders (Fig. 10). Granular cell tumors are characterized by sheets of large and polyhedral eosinophilic cells,

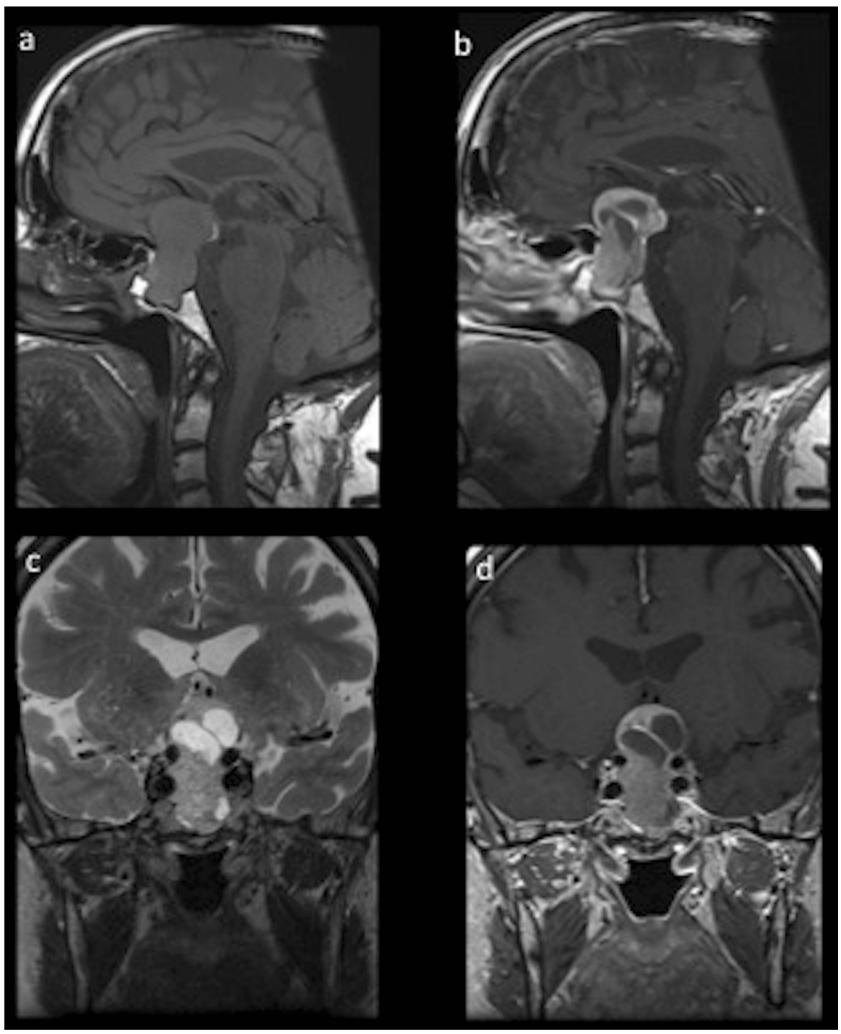

Fig. 9 Sagittal (**a** and **b**) and coronal view (**c** and **d**) of a huge sellar lesion with a suprasellar multiloculated cystic part, provoking a compression of the optic chiasm and a displacement of the floor of the third ventricle. The sphenoid sinus was also invaded. The contrast enhancement (**b** and **d**) was strong and the bright spot corresponding to the posterior pituitary was displaced superiorly toward the infundibulum (**a**). Pathology revealed a granular cell tumor

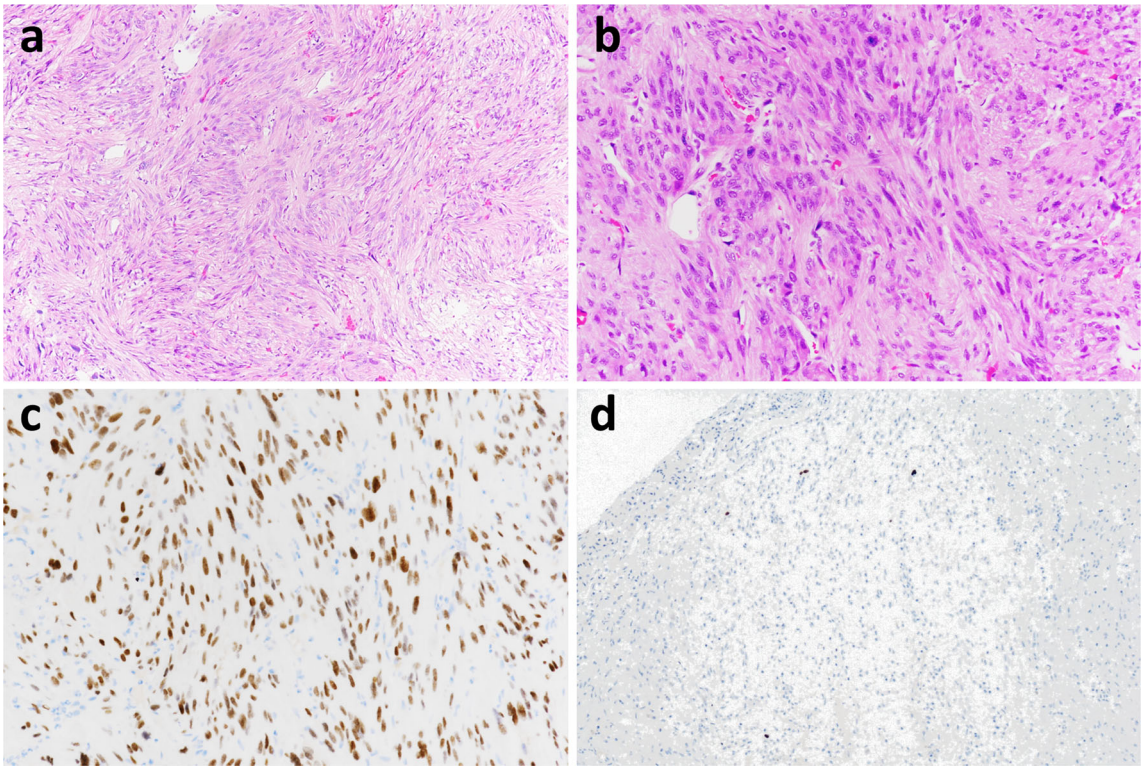

Fig. 10 Pituicytoma showing a storiforme pattern of growth (**a**) composed of spindle cells (**b**) positive for TTF1 (**c**). The Ki67-proliferative index is very low (**d**)

containing PAS-positive granules (Fig. 11). Spindle cell oncocytomas are characterized by a proliferation of cells forming poorly defined lobules. As a general rule, all these variants show minimal nuclear atypia and mitoses are inconspicuous or absent. All these tumors are invariably negative for pituitary hormones, cytokeratins, synaptophysin, chromogranin A, neurofilaments, CD34, BCL-2, smooth muscle actin, and desmin. They are variably positive for vimentin, CD68, α_1-antitrypsin, cathepsin B, galectin-3, EMA, GFAP, and S100. However, the hallmark of all these entities is the nuclear immunoreactivity for TTF-1 [23]. The Ki67 proliferative index is usually low. The differential diagnosis may vary: pituicytomas may mimic pilocytic astrocytomas while oncocytic and granular cell variants may mimic pituitary adenomas. Immunohistochemistry is mandatory to perform the differential diagnosis.

Oncological Illnesses

In a patient with known oncologic illness and especially with a history of DI, a pituitary metastasis should be suspected. *Pituitary metastases* account for less than 1% of intracranial metastases and about 1% of pituitary tumors. Their prevalence is increasing because of the improved overall survival of

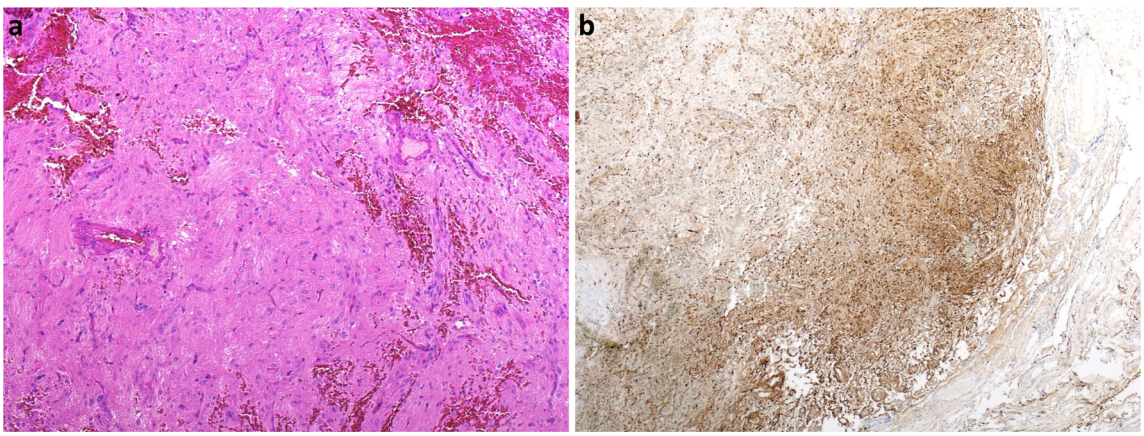

Fig. 11 Granular cell tumors characterized by sheets of large and polyhedral eosinophilic cells (**a**) positive for S100 (**b**)

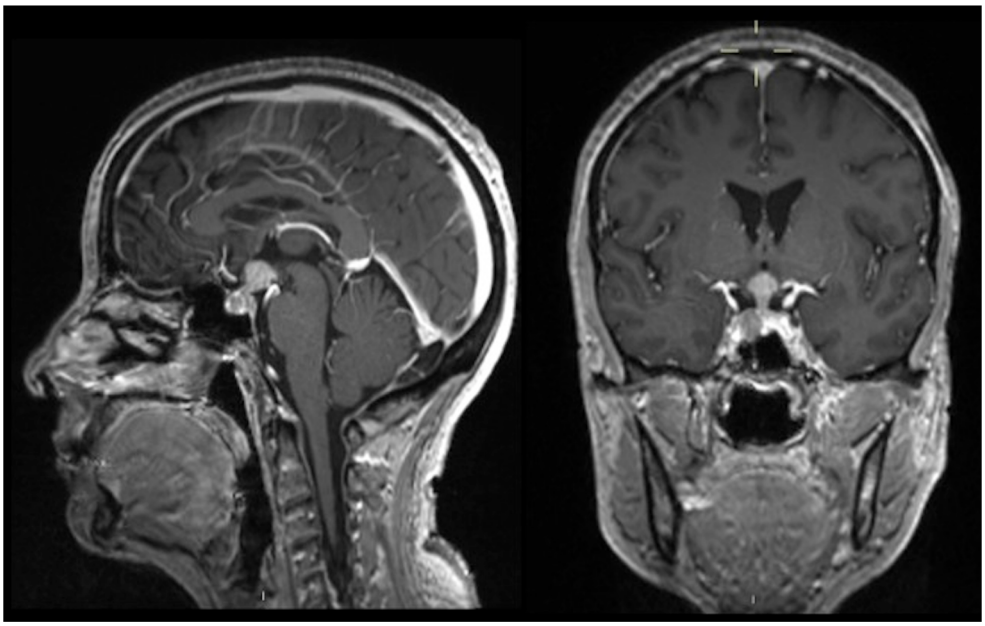

Fig. 12 T1-weighted cerebral MRI after gadolinium administration in the sagittal (left) and coronal plane (right) showing a sellar lesion with a suprasellar extension and probable infiltration of the pituitary stalk. The diaphragm opening is small and the lesion has an hourglass shape. The contrast enhancement is strong and heterogeneous and the lateral limits are not well defined and a bilateral cavernous sinus invasion was present. The posterior bright spot is absent. The pathology was consistent with a pituitary metastasis of a mammary adenocarcinoma

oncologic patients and about 2% of patients with known malignancies present latent pituitary metastases at autopsy [24, 25]. Epidemiology reflects that the most frequent primary tumors are those from the lung and breast followed by colon, prostate, and kidney [26, 27]. The more frequent posterior location of metastases is probably due to the hematogenous spread through the direct arterial supply of the neurohypophysis (portal circulation) [24, 25]. The radiological differential diagnosis between pituitary metastases and the more common pituitary adenomas is a challenging task and the characteristics

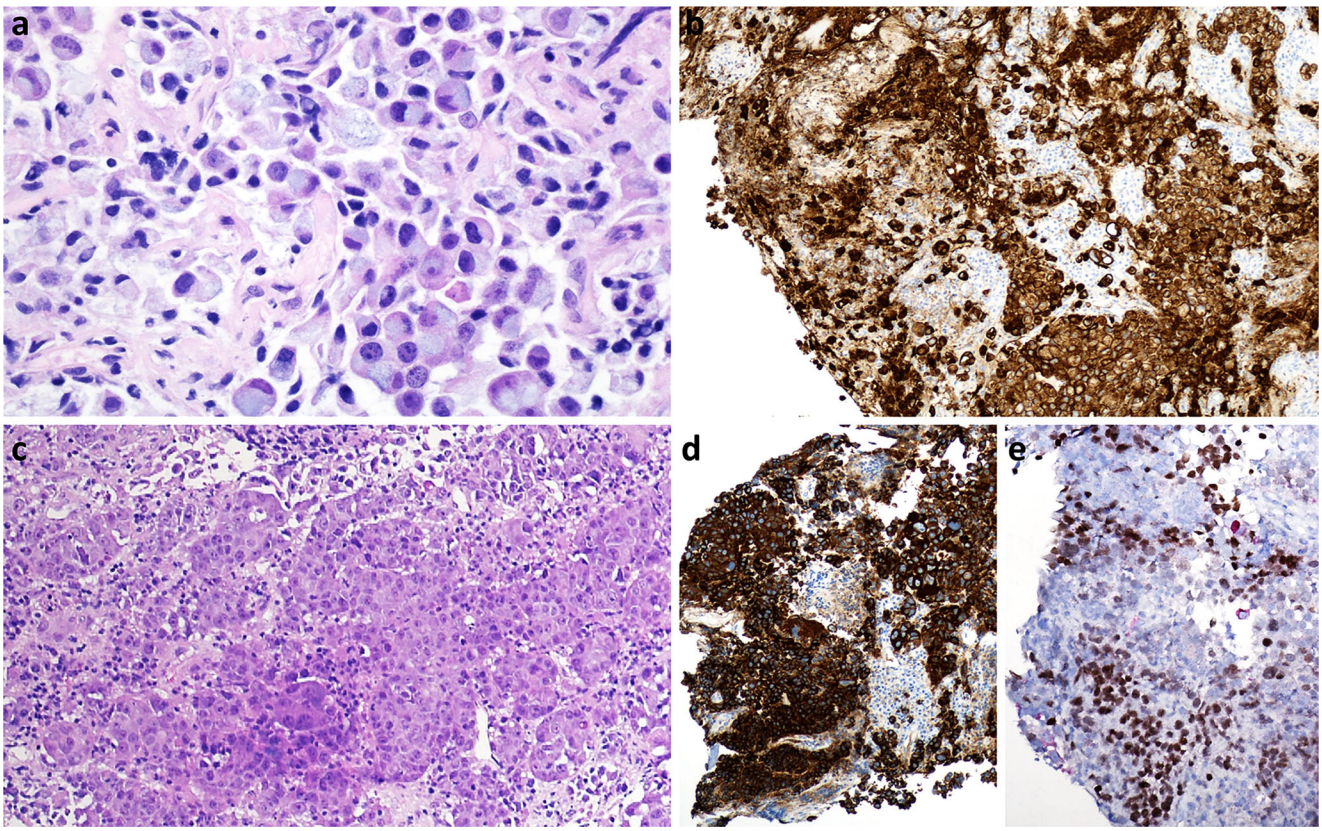

Fig. 13 Pituitary metastasis from a breast carcinoma with a signet ring cell component (**a**) strongly positive for cytokeratin 7 (**b**). Pituitary metastasis from a lung adenocarcinoma (**c**) showing immunoreactivity for cytokeratin 7 (**d**) and TTF1 (**e**)

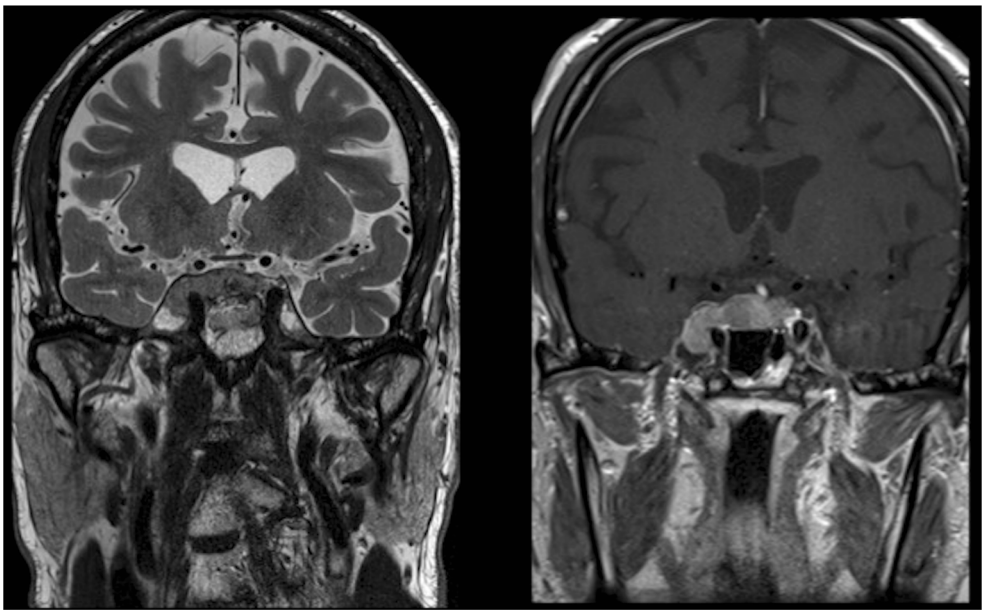

Fig. 14 T2-weighted (left) and T1-weighted (right) coronal MRI show a sellar lesion with an important cavernous sinus invasion on the right side The contrast enhancement is important and heterogeneous (right) and the stalk and the normal pituitary are displaced on the left portion of the sella. Pathology confirmed a pituitary lymphoma and because of the absence of other cerebral or systemic localization, the diagnosis of primary pituitary lymphoma (PPL) was retained

that help in diagnosing a pituitary metastases are summarized in Table 3 and Fig. 12. The pathological and immunohistochemical features depend on the primary neoplasm (Fig. 13). An early diagnosis is important and the management is based on a multimodal approach including surgery, radiotherapy, and chemotherapy. Surgery is generally performed in the presence of neurological deficits (such as visual symptoms) and in cases of uncertain diagnosis. Only 10% of patients are still alive at 1 year from diagnosis [25].

In any patient with immunosuppression, especially in presence of a DI, *primary pituitary lymphomas* (PPLs) should be considered among the differential diagnosis. Radiological features of pituitary lymphomas are detailed in Table 3 and Fig. 14. PPL are most commonly B-cell lymphomas (> 80% of cases) with diffuse large B-cell lymphoma (DLBCL) being the most frequent histotype (63%) (Fig. 15). Burkitt lymphoma, T-cell lymphoma, MALT lymphoma, and primary pituitary plasmocytoma have been reported as well. Immunohistochemistry is mandatory for the differential diagnosis among different types of lymphomas and for the differential diagnosis with non-neoplastic lesions such as hypophysites [28]. The mean overall survival is poor for patients with PPL (14 months) [29].

Non-neoplastic Pathologies

In addition to neoplastic diseases, non-neoplastic pathologies should be considered in the differential diagnosis of sellar lesions with or without endocrine symptoms. *Hypophysitis* accounts for approximately 0.4% of pituitary surgery cases [1] with an annual incidence of 1 in 7–9 million [30]. They include lymphocytic and granulomatous hypophysitis, xanthomatous hypophysitis, and IgG4-related hypophysitis (RH). Lymphocytic hypophysitis (LH) is the most frequent hypophysitis: it represents an autoimmune disease [31, 32] and is generally secondary to the spreading use of immunotherapy. Granulomatous hypophysitis is the second most frequent type and can be primary or secondary to a systemic granulomatous disease [33–35]. The xanthomatous hypophysitis is characterized by the infiltration of the anterior

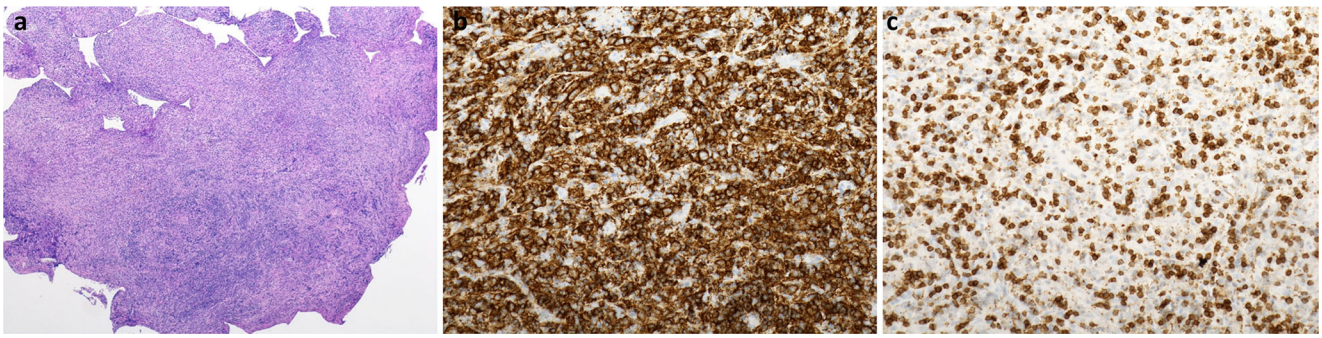

Fig. 15 Massive infiltration of the pituitary gland by a diffuse large B-cell lymphoma (**a**) strongly positive for CD20 (**b**). Several reactive CD3 positive T lymphocytes are also observed (**c**)

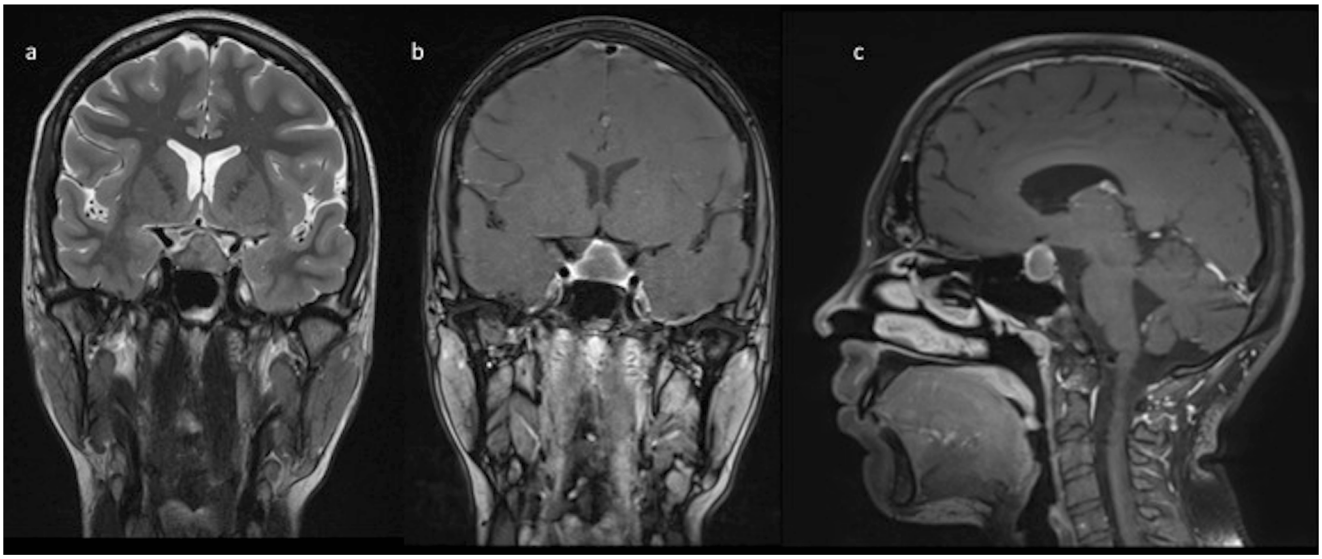

Fig. 16 Coronal (**a** and **b**) and sagittal (**c**) views of T2-weighted (**a**) and T1-weighted (**b** and **c**) cerebral MRI showing a sellar lesion with a symmetric pituitary enlargement. The normal pituitary is not visible and the stalk is not deviated. The classical shape of hypophysitis with thickening of the stalk is here evident. Pathology confirmed this diagnosis

pituitary by foamy histiocytes. Its etiology is unclear and it seems to be related to the rupture of a Rathke's cleft cyst [36] or to the presence of craniopharyngioma [37]. IgG4-RH is generally considered as part of a systemic disease also known as IgG4-related disease [38]. The diagnosis is based on the measure of serum IgG4 serum level [39] and on the demonstration of IgG4-positive plasma cell infiltration [40]. It has recently been suggested that IgG4-RH is a heterogeneous disease with gender-related characteristics: females are affected in their second–third decade of life, with a solitary pituitary lesion, low IgG4 serum level, and frequent association with autoimmune disorders. By contrast, men are elderly, often with a systemic IgG4-related disease and high IgG4 serum levels [41]. Radiological features are reported in Table 3 and illustrated in Fig. 16. LH may also present aggressive radiological features such as invasion of the cavernous sinus and obliteration of both internal carotid arteries [42]. Although different histologic subtypes of hypophysitis are well defined [43], a mixed histology may be occasionally encountered [44]. LH is characterized by a predominant lymphocytic infiltration, which may only involve the anterior or posterior lobe and the stalk or the whole gland. [31]. Histological detection of lymphocytes within the pituitary gland remains the diagnostic hallmark. The granulomatous form (Fig. 17) presents a variable amount of fibrosis and lymphocytic infiltration and it characterized by widely distributed multinucleated giant cells

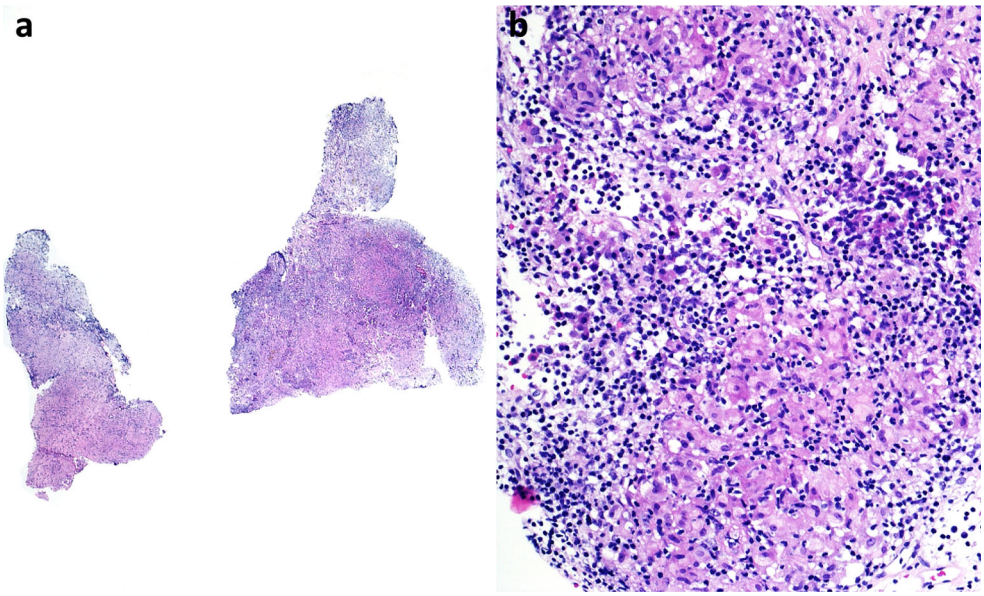

Fig. 17 In granulomatous hypophysitis, the pituitary gland is substituted by a variable amount of fibrosis and lymphocytic infiltration (**a**) with widely distributed, well-formed granulomas (**b**)

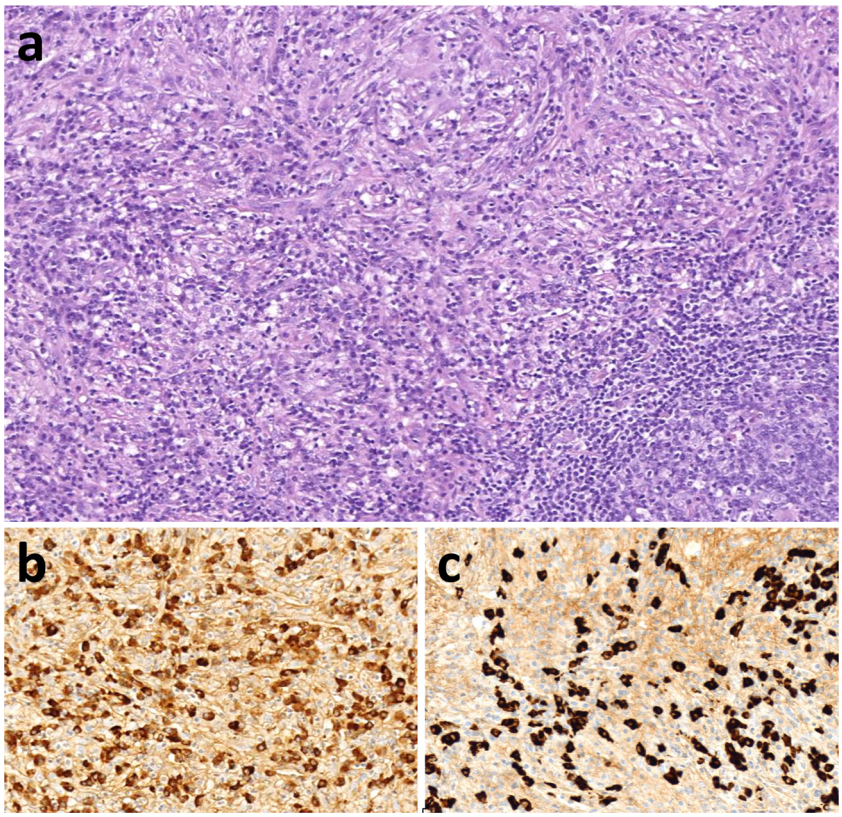

Fig. 18 (**a**) IgG4-related hypophysitis is characterized by a prominent lymphocytic infiltration with formation of germinal center (right bottom corner) and storiform fibrosis. Typically, the IgG4/IgG ratio is increased. IgG (**b**) and IgG4 (**c**) immunostainings

[45]. Xanthomatous hypophysitis presents the characteristic infiltration of the anterior pituitary gland by foamy histiocytes with a lipid content [46]. The IgG4-related hypophysitis is characterized by a prominent lymphocytic infiltration, storiform fibrosis, and IgG4-positive plasma cells with increased IgG4/IgG ratio (Fig. 18).

Pituitary hyperplasia (PH) is physiological during pregnancy due to lactotroph proliferation. Pathological hyperplasia can be idiopathic or consequent to an abnormal stimulation by hypothalamic hormones [48] or secondary to medication intake [49–51]. It is secondary to non-neoplastic polyclonal proliferation of a specific adenohypophyseal cell subtype [47]. Epidemiological data are scarce as the number of cases of PH reported in literature is extremely limited [48, 52]. Clinical manifestations may be highly variable and the hyperplasia of each anterior pituitary cell type can give rise to the same clinical syndromes observed in pituitary adenomas. A diffuse and symmetrical pituitary enlargement is typical for PH which appears isointense to the gray matter and the contrast enhancement is homogeneous. The normal pituitary gland is not

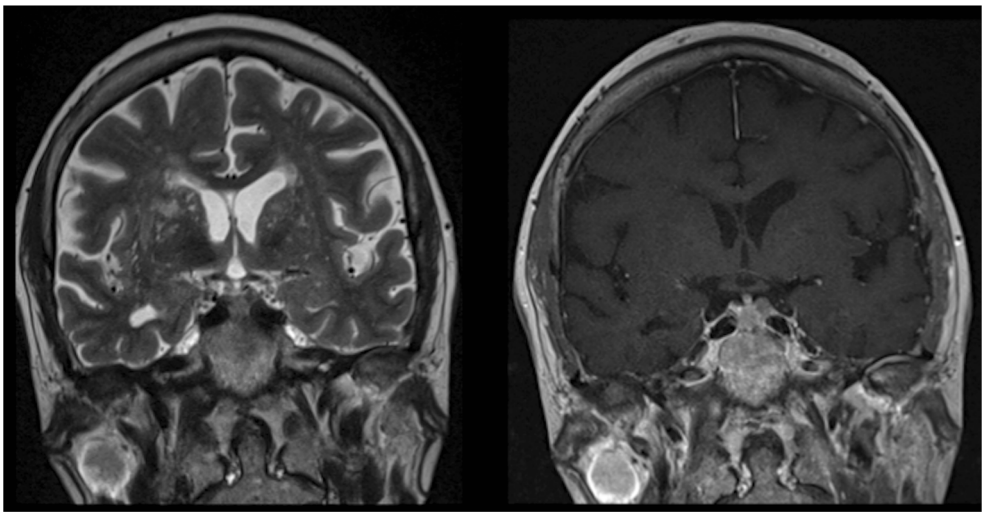

Fig. 19 Coronal views of a T2-weighted (left) and T1-weighted cerebral MRI after gadolinium administration (right) showing an enlargement of the pituitary gland with a homogeneous contrast enhancement (right) and no displacement of the stalk. No suprasellar or parasellar extension was present. Pathology showed a pituitary hyperplasia

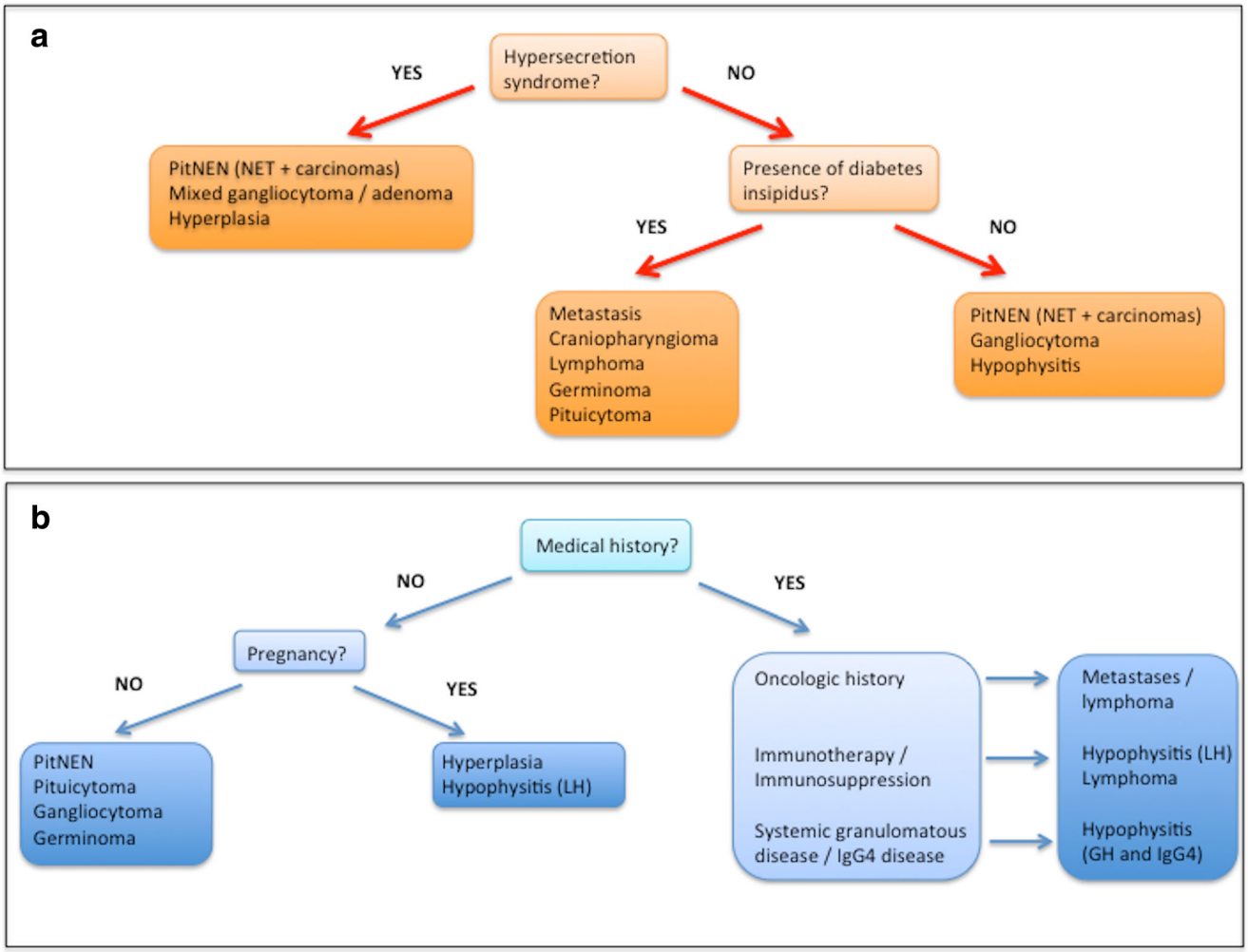

Fig. 20 The presence of hypersecretion syndrome and/or diabetes insipidus may guide the diagnostic pathway (**a**). A history of oncologic illnesses, immunosuppression, and pregnancy may help in guiding the diagnosis (**b**). GH, granulomatous hypophysitis; LH, lymphocytic hypophysitis; PitNEN, pituitary neuroendocrine neoplasms

identifiable [52, 53] (Table 3 and Fig. 19). The most important differential diagnosis is with pituitary adenoma and relies on the intact reticulin network, which is observed in PH and lacks in adenomas [54]. Using immunohistochemistry, it is possible to demonstrate entrapped normal pituitary cells within the dominant hyperplastic cells. Cell proliferation is very low, so the use of proliferation markers does not help in diagnosis [53].

The recognition of this rare pituitary lesion may avoid unnecessary surgeries as PH rarely progress and the correction of the underlying cause may cause the regression.

Rare pituitary lesions represent less than 5% of this surgical series. A good understanding of these pathologies is essential in formulating the ideal diagnostic and therapeutic plan. The clinical features that would help suspect a non-PitNET lesion include diabetes insipidus, prior medical illnesses, and pregnancy with or without hormonal hypersecretion (Fig. 20). The histopathological analysis, however, remains the mainstay to determine the treatment goals and prognosis.

Compliance with Ethical Standards

Conflict of Interest None.

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