Multiple Tumorous Lesions of The Pituitary Gland

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Research Article

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Abstract

Multiple tumorous lesions with an adenoma make up 1.4 % (232 cases) in the large collection of the German Registry of Pituitary Tumors. 2.0% of all PitNETs are associated with a second lesion. Within the selected cases synchronous multiple pituitary neuroendocrine tumors (PitNETs) account for 17,3%, PANCH cases for 14.7%, PitNETs and posterior lobe tumors for 2.2%, PitNETs and metastases for 5.2%, PitNETs and mesenchymal tumors for 2.6%, PitNETs and cysts for 52.2% and PitNETs and primary inflammation for 6.0%. The mean patient age was 53.8 years with a standard deviation of 18.5 years. 55.3% of the patients were female and 44.7% were male. From 1990 to 2018 there was a continuous increase in the number of multiple tumorous lesions.

Introduction

Pathohistological examinations of surgical specimens of the pituitary show in the vast majority of cases only one lesion [1]. In a small number of cases however a second lesion coexisted, so that in 2017 the diagnosis of synchronous multiple pitNETs was included for the first time in the WHO classification [2].

Multiple lesions represent two or more morphologically separated lesions. In the pituitary gland, the pituitary neuroendocrine tumors is the most common neoplasm [3].

The secondary lesion besides an PitNET can be neoplastic, vascular, congenital, or inflammatory [4].

So far, there is no common pathogenetic explanation for the coexistence of two separate lesions. Since many cases of double lesions have been described in the literature a random coexistence might be doubted.

The aims of our studies were descriptions of coincidental different lesions in the pituitary, especially their types and numbers to answer the question whether typical combinations or random coincidences exist.

Material And Methods

The German Registry of pituitary tumors with its cases from 1990 to 2018 served as the database. The registry was unofficially founded by one of the authors (WS) in 1970. It serves to a collection of all surgical and autoptical specimens from the pituitary that are send for pathohistological routine work to the Institute of Pathology of the University Hospital Eppendorf during the years 1970 to 1978 and since 2013 and during the years 1979 to 2012 to the Institute of Pathology of the Marienkrankenhaus Hamburg. It has been officially founded by the German Society of Endocrinology in 1995 as the German Registry of Pituitary Tumors. With a total of 16.449 cases by the end of 2018, it represents an incomparably large collective. Of these cases 12.673 originate from surgical and 3.611 from autopsy material.

During pathohistological preparation, the specimens were fixed in formalin and embedded in paraffin. The sections were stained with hematoxylin-eosin and PAS.

Monoclonal (Prolactin, TSH, FSH, LH, α subunit) or polyclonal (GH, ACTH) antibodies were used to detect pituitary hormones in the lesions.

Since 2017, antibodies against the transcription factors Pit-1, T-Pit and SF-1 were used in difficult cases. The criteria of the new WHO classification of 2017 were the basal principles for classification since 2018 [2].

For differentiation of other sellar tumors, such as meningiomas, chordomas or metastases, it may have been necessary the use of additional antibodies was necessary. For these cases, a broad antibody spectrum could be used.

Autopsy pituitaries were generally studied by HE and PAS sections. If any lesions were demonstrated in these specimens additional immunostainings were performed.

Results

A total of 232 cases (1.5 % of the collection) with multiple tumorous lesions were selected out of the registry. Of these, 38 were double PitNETs, two triple PitNETs, 34 PitNETs next to a gangliocytoma, five PitNETs next to neurohypophyseal tumors, twelve PitNETs besides or within metastases, six PitNETs next to mesenchymal tumors, 121 PitNETs next to cysts and 14 adenomas next to primary inflammations.

70% of all cases in the registry are associated with PitNETs.

Of these, 2.04% are associated with another lesion. In the last few decades, there has been a slight increase in the number of diagnoses of multiple lesions. In percentages, more double lesions were diagnosed in post-mortem material (1.61%) than in the surgical material (1.13%) (Table 1).

Table 1
Multiple lesions in surgical and autopsy material

Cases (surgical and autopsy material)	Amount	Autopsy ([%] of all autopsy cases)	Surgical ([%] of all surgical cases)
Double PitNETs	38	21 (0,58)	17 (0,13)
Triple PitNETs	2	2 (0,06)	0 (0)
PitNET and gangliocyoma (PANCH)	34	0 (0)	34 (0,27)
PitNET and posterior lobe tumor	5	2 (0,06)	3 (0,02)
PitNET and metastasis	12	6 (0,17)	6 (0,05)
PitNET and meningeoma	6	2 (0,06)	4 (0,03)
PitNET and cysts	121	25 (0,69)	96 (0,76)
PitNET and primary Inflammation	14	1 (0,03)	13 (0,1)
Total	232	59 (1,61)	173 (1,13)

The patient's age at the time of the operation was on average 53.8 years with a standard deviation of 18.5 years. 45 % of the patients are male and 55 % female.

Double PitNETs were found quantitatively similarly frequently in post-mortem and surgical material (Table 1). However, the proportion of cases in autopsy specimen is comparatively higher (0.58% vs 0.13%). The cases of a PitNET and a gangliocytoma were all diagnosed in the surgical material.

The most common type in double lesions is the PitNET sparsely granulated prolactin cell (22.5%). Compared to the tumor registry (8.9%), prolactin-secreting PitNETs in multiple lesions are more common. Null cell adenomas make up 21.1% in our study, although this proportion would be much lower according to the current WHO classification with its new definition of null cell adenomas [2].

It is also noticeable that gonadotrophic PitNETs represent the largest proportion in the tumor registry with 31.0%, but only 16.7% in multiple lesions.

ACTH-secreting PitNETs make up 12% of the adenomas in multiple lesions. In the tumor registry, this percentage is 16.2%. GH-secreting PitNETs and mixed GH- / Prolactin-secreting PitNETs make up a total of 23.3% of PitNETs in double lesions and 21.47% in the whole tumor registry.

TSH-secreting PitNETs, α -subunit PitNETs, plurihormonal PitNETs and unclassifiable PitNETs occur only sporadically in multiple lesions (together 3.3%) and thus appear with a similarly low probability as in the whole tumor collection (together 4.02%).

Multiple PitNETs

From 1990 to 2018, 38 cases with multiple PitNETs were described in the German Registry of Pituitary Tumors. 21 of these cases were diagnosed in post-mortem and 17 in surgical specimen. Significantly more men (68%) than women (32%) were affected by double PitNETs. 0.5% of all PitNETs in the database are in coexistence with second PitNET.

Within the double PitNETs, sparsely granulated prolactin cell tumors make up the largest proportion (25.0%). This is followed by null cell adenomas (23.68%), FSH / LH, FSH or LH tumors (17.1%), mixed GH /Prolactin tumors (10.5%), sparsely granulated and densely granulated ACTH tumors (both 7.9%), densely granulated GH tumors (5.26%), TSH tumors (1.3%) and unclassifiable tumors (1.3%).

The cell lines of the coexisting PitNETs were compared with a cross table to visualize overlaps (Table 2). Ten PitNETs out of 76 coexisted with the same cell line. In 36 PitNETs the cell lines are certainly different and in another 30 PitNETs the cell line cannot be determined with certainty. The cases which could not be determined with certainty contain null cell adenomas, due to lack of determination of transcription factor.

Table 2
combinations of transcription factors in multiple PitNETs

Cell line first PitNET [N]	Cell line second PitNET [N]				total
	TPIT	PIT1	SF1	not definable	
TPIT	0	7	3	2	12
PIT1	7	10	8	8	33
SF1	3	8	0	1	12
not definable	2	8	1	8	19
total	12	33	12	19	76

The Chi-square test according to Pearson supports the null hypothesis and states that there is no significant correlation between the cell line combinations (Chi-square test, $p = 0.063$, $n = 76$).

Clinical data were available in 33 of 38 cases. In 14 cases the PitNETs were clinically inactive, in nine cases acromegaly was present, in two cases increased IGF-1 levels were documented, in six cases hyperprolactinemia was present and in two cases patients suffered from Cushing's disease.

Women diagnosed with a double PitNETs showed clinical signs of acromegaly (including increased IGF-1 levels) in 41.3% of cases. Cushing's disease was present in 16.7% of women.

Men with a double PitNETs had acromegaly in 24.0% (including increased IGF-1 levels). In 36% of cases the PitNETs were inactive and in 20% hyperprolactinemia was present.

Three cases from 1991, 2003 and 2006 were identified in which three PitNETs coexisted next to each other. In all cases the diagnoses were made post-mortem.

Two of the cases were diagnosed in female patients and one in a male patient.

In the cases of triple PitNETs, there was a coexistence between three null cell adenomas, a coexistence between two null cell adenomas and one TSH tumor, and in the third case two LH cell tumors and one null cell adenoma. All nine PitNETs were microadenomas (maximum diameter less than 1 cm) that were completely separated from each other.

11.8% of the total of 85 multiple PitNETs are combinations with the same transcription factor, 42.4% are tumor combinations with different transcription factors and 35.3% have a null cell adenoma in the tumor combination, so that due to the lack of transcription factor determination no statement could be made regarding the cell line (Table 3).

Table 3
Combinations of multiple PitNETs

	PitNETs [N]	Proportion [%]	Cases [N]
Triple PitNETs of the same subtype	3	3,5	1
Triple PitNETs (2x same subtype, 1x different subtype)	6	7,0	2
Double PitNETs with the same transcription factor	10	11,8	5
Double PitNETs with different transcription factors	36	42,4	18
Double PitNETs with unidentifiable transcription factors	30	35,3	15
Total	85	100,00	41

Adenoma and Gangliocytoma (P ituitary Adenoma Neural Choristoma = PANCH)

34 cases with the combination of a PitNET and a gangliocytoma were diagnosed in the database. All cases were identified in surgical specimens. There are significantly more women (76.5 %) affected by PANCH cases than men (20.6 %) (Exact binominal test, two-sided, $p = 0.001$, $n = 33$).

88.2% of PANCH cases were associated with a GHRH containing gangliocytoma. Of 34 identified cases, 31 tumors were PIT-1 positive. Two PitNETs originate from the T-Pit cell line and in one case, the cell line cannot be determined because it is a null cell adenoma (Table 4).

Table 4
Combinations of PitNET and gangliocytoma type

PitNET-Subtypes (surgical material)	Gangliocytoma	Amount	Percent [%]
Sparsely granulated GH-cell	GHRH	9	26,5
Mixed GH/Prolactincell	GHRH	20	58,8
Sparsely granulated Prolactincell	not reliably determinable	2	5,9
Densely granulated ACTHcell	CRH	1	2,9
Densely granulated ACTHcell	not reliably determinable	1	2.9%
Nullcell	GHRH	1	2.9%
Total		34	100%

The proportion of Pit-1-positive tumors is 91.2%.

Clinically, acromegaly was diagnosed in 82.4% of PANCH cases. Cushing's disease was present in 2.9%, hyperprolactinemia in 5.9% and the clinic was unremarkable in 8.8%.

PitNET and posterior lobe tumor

Five cases with a combination of a posterior lobe tumor and a PitNET were diagnosed in the database. The cases were diagnosed between 2007 and 2018.

8.3% of all spindle cell oncocytomas, 10% of all pituicytomas and 11.1% of all granular cell tumors are associated with a coexistent adenoma. Together 10% of all posterior lobe tumors in the tumor registry are in coexistence with an adenoma (Table 5).

Table 5
Posterior lobe tumor in the German Registry of Pituitary Tumors

Posterior lobe tumor	Cases from 1990–2018	% of non-PitNETs (n = 1953)	% of all cases (n = 11631)	% in combination with a PitNET (cases)
Spindlecell oncocytoma	12	0,61	0,10	8,33 (1)
Pituicytoma	20	1,02	0,17	10,0 (2)
Granular cell tumor	8	0,92	0,15	11,1% (2)
Total [N]	50	2,56	0,42	10,0% (5)

The following combinations were selected:

- PitNET sparsely granulated GH and a granular cell tumor
- PitNET sparsely granulated prolactin and a granular cell tumor
- PitNET sparsely granulated prolactin and a pituicytoma
- null cell adenoma and a pituicytoma
- null cell adenoma and a spindle cell oncocytoma

PitNET and metastasis

12 cases with the combination of a PitNET and a metastasis were identified. Six cases were diagnosed in surgical and six cases in post-mortem specimens. Patients with this tumor combination had an average age of 70.3 years. From these 75 % were male and 25% female.

In the database are 112 cases of metastasis which means that in 10.7% of these cases a coexistent PitNET was present.

In five cases the metastasis originates from a lung tumor, in two cases from a kidney tumor and in single cases from a malignant melanoma, a tumor of the prostate or a sinunasal tumor. In one case the origin is not clear.

The distribution of the metastasis types reveals three cases with an adenocarcinoma and each time two cases of with small cell carcinoma, with undifferentiated carcinoma and clear cell carcinoma.

In single cases a malignant melanoma and a squamous cell carcinoma were diagnosed (Table 6).

Table 6
Combination of PitNET and metastasis

PitNET subtypes	Examination material	Localization	Metastasis	Origin
Densely granulated GH tumor	Surgery	PitNET	Adenocarcinoma	Sinunasal
GH/Prolaktin-tumor	Post-mortem	Posterior lobe	Malignant melanoma	Skin
Sparsely granulated Prolactin tumor	Surgery	PitNET	Undifferentiated carcinoma	Unknown
Sparsely granulated Prolactin tumor	Post-mortem	Capsule	Small cell carcinoma	Lung
Densely granulated ACTH tumor	Surgery	PitNET	Clear cell carcinoma	Kidney
Densely granulated ACTH tumor	Post-mortem	Capsule	Scirrhou carcinoma	Gastric
FSH/LH-, FSH- or LH-tumor	Surgery	PitNET	Adenocarcinoma	Prostate
FSH/LH-, FSH- or LH-tumor	Post-mortem	Posterior lobe and sinus cavernosus	Squamous cell carcinoma	Lung
FSH/LH-, FSH- or LH-tumor	Surgery	PitNET	Clear cell carcinoma	Kidney
FSH/LH-, FSH- or LH-tumor	Surgery	PitNET	Adenocarcinoma	Lung
Null cell tumor	Post-mortem	Capsule	Undifferentiated carcinoma	Lung
Plurihormonal tumor	Post-mortem	Capsule, anterior lobe and in PitNET	Small cell carcinoma	Lung

Of the selected twelve cases, metastasis was found in seven cases within the coexistent PitNET. The pathohistological transition between the PitNET and the metastasis was described fluently. It is remarkable that in all surgical cases the metastases were found within the PitNET.

In further three cases the metastasis was in the capsule and in two cases in the posterior lobe.

Accordingly, 58% of the cases the metastasis was localized within the PitNET and in 42% it was separated from the PitNET. This percentage difference is not statistically significant (Exact Binomial Test, bilateral, $p = 0.774$, $n = 12$).

Adenoma and cysts

From 1990 to 2018 121 cases of cysts besides PitNETs were identified. 25 cases were diagnosed post-mortem and 96 cases in surgical specimens.

In total 583 cysts were diagnosed in the German Registry of Pituitary Tumors. Consequently 20.7 % of all cysts are in coexistence with a PitNET.

16.6 % of all Rathke's cleft cysts, 7.6% of colloid cysts, 9.5% of arachnoid cysts and 36.7 % of unclassifiable cysts are associated with a coexistent PitNET (Table 7).

Table 7
Cysts in the German registry of pituitary tumours from 1990–2018

Type of cyst	Amount	% of non-PitNETs	% of all cases	Cases in multiple lesions (Proportion of subgroup in relation to the total collective [%])
Rathke's cleft cyst	441	9,03	2,71	73 (16,55)
Colloidcyst	66	1,35	0,41	5 (7,58)
Arachnoid cyst	21	0,43	0,13	2 (9,52)
Unclassifiable cyst	30	0,61	0,18	11 (36,67)
Total	583	11,93	3,59	91 (15,61)

Rathke's cleft cysts and PitNETs make up the largest group, with 73 identified cases. In eight of these cases there was an additional concomitant inflammation. In 28.8% of the cases the Rathke's cleft cyst was combined with a gonadotrophic, in 21.9% with a sparsely granulated prolactin cell tumor and in 17.8% of the cases with a null cell adenoma. The remaining cases are divided into small groups and different PitNET types.

PitNET and meningioma

Six cases of meningioma and PitNET were identified during the study period. In the pituitary tumor register, meningiomas account for 0.9% of all cases. 4.0% of all diagnosed meningiomas – one of them was malignant - are accompanied by a coexistent PitNET.

All meningiomas found in coexistence to a PitNET were meningiomas of WHO grade 1.

No abnormal frequency was found in the PitNET distribution.

PitNET and primary inflammation as tumor-like lesions

From 1990 to 2018 we identified 14 cases with the combination of a primary inflammation and a PitNET.

Of these 14 cases, nine cases were combined with lymphocytic hypophysitis. In three cases granulomatous hypophysitis was present. In one case each there was a combination of an abscess or a xanthogranuloma and a PitNET.

Clinically, six cases were inactive, in three cases compression were present and in one case the PitNET was hormonally active (TSH-secreting PitNET).

The two GH secreting PitNETs were associated with acromegaly.

Discussion

Multiple pituitary lesions are becoming increasingly important in pathohistological and therefore also in preoperative diagnostics. If clinical symptoms do not change after surgery or if the pathohistological specimens does not match the clinical findings an undetected further lesion might be the reason. Multiple lesions can also provide information on the pathogenesis of solitary lesions. Therefore, they represent an important research contribution to tumorigenesis.

In the pathohistological specimens of unselected post-mortem pituitaries PitNETs show a prevalence of 10 % to 14.4 % [5; 6].

If this prevalence is related to the 3611 autopsy cases in the pituitary tumor registry, 361 to 520 PitNET-cases are to expect within the group of post-mortem examined cases. Since in our study 59 autopsy cases were associated with a multiple lesion, this would correspond to a prevalence of 11.3 to 16.3% for the presence of a coexistent secondary lesion in addition to a PitNET using the data from studies of Ezzat et. al. and Buurman and Saeger [5; 6]. Consequently because of these high percentages the actual number of multiple lesions might be higher than reported in our data and in the literature.

Further it illustrates the importance of multiple lesions in clinical and pathohistological routine. Whether these two lesions are randomly coexisting or arising from one origin needs to be taken a closer look on.

Multiple PitNETs

Studies on surgical material report prevalences between 0.3 to 1.3% for multiple PitNETs [7; 8; 9]. In our collective multiple PitNETs account for 0.66% of all PitNETs. Therefore, our data are within the framework in the literature. In our unselected autopsy series multiple PitNETs occur with a prevalence of 0.58%. Comparable studies report a slightly higher prevalence of 0.9% [10].

In our study men are affected significantly more often than women. In comparable studies, equivalent gender ratios [11] or even a female predominance have been described [12]. On this base, the male predominance in our study may also be due to random chance.

In the literature, GH secreting PitNETs have most frequently been diagnosed in pituitaries with multiple PitNETs [10, 11].

Recent studies describe increasing numbers of ACTH-secreting PitNETs in patients with multiple PitNETs [15].

Because of the high number of GH- and ACTH-secreting tumors, multiple PitNETs are often associated with the symptoms of acromegaly or Cushing's disease [11]. In the surgically removed specimens in our collection, symptoms of acromegaly were described in 64.7% and symptoms of Cushing's disease in 11.8% of the cases.

Due to the high prevalence of acromegaly in multiple PitNETs, it may be interesting to perform IGF-1 screening when a multiple PitNETs is suspected.

Multiple PitNETs have been listed in the WHO classification of endocrine tumors since 2017 [2]. Multiple PitNETs need to have different cell lineages to be classified as those.

If it can be predicted by the examination material that the two coincident lesions coexist separately from each other, cases in which the same cell lineage is present should also be listed as multiple PitNETs.

Etiologically there are different theories that are used for the genesis of multiple PitNETs.

For example, in multi-hit theory, it is assumed that two mutated monoclonal pituitary cell types coincidentally give rise to two tumors to develop simultaneously [13].

Other authors assume that one PitNET can induce the development of another via growth factors [4]. This theory is especially associated with GH-secreting tumors [8].

In summary, the etiology of multiple PitNETs is thought to be like that of solitary PitNETs. Therefore, it is still most likely that multiple PitNETs are formed by random events. This hypothesis is also supported by the data we select.

PANCH-Cases

PANCH cases are of special interest because of the smooth transition between the lesions and the influence of the origin of the lesions on each other.

PANCH cases occur in the tumor registry with a prevalence of 0.21%. Yang et al. have reported a prevalence of 0.46% out of 4317 cases for PANCH cases in their study [14]. Other studies calculated prevalences from 0.52 to 1.26% [15; 16].

The comparable studies only examined surgically removed specimens. Since all the PANCH cases in our study were found in surgical material, the prevalence can also only be related to the surgical database, resulting in a slightly increased prevalence of 0.26%.

Comparable to Yang et al. (65% female), we found significantly more women (78.8%) with PANCH cases than men [14]. The cause of this distribution is still unknown. In comparable acromegaly studies, no abnormal gender distribution was found [17].

82.4% of the PANCH-cases have been diagnosed with acromegaly. The proportion of acromegaly cases is lower in comparable studies. According to the study from Yang et al., 75% of PitNETs were sensitive to GH, while only 25% were clinically diagnosed with acromegaly. [14].

It is likely that the two lesions affect each other pathogenetically due to the releasing factor of the gangliocytoma [15; 18; 19]. The close relationship between the two lesions is also illustrated by the possible transition of gangliocytoma cells into PitNETs cells and vice versa (Fig. 1) [18]. Only 5.6% of gangliocytomas in the Tumor Registry are solitary. In the literature it is estimated that 65–85% of all pituitary gangliocytomas coexist with a PitNET [20].

Posterior lobe tumor and PitNET

PitNETs besides posterior lobe tumors are very rare but probably underdiagnosed processes in the tumor registry and as well as in the literature. The combination of a neurohypophyseal tumor and a PitNET was first described by Neidert et al. in 2016 [21]. In the German Registry of Pituitary Tumors the first case of this combination was documented in 2007.

Due to the posterior position of the neurohypophyseal tumor, it may not be detected during the operation. 10% of all posterior lobe tumors in the Tumor Registry are associated with a coexistent PitNET. They are listed in recent classifications as TTF-1 expressing spindle cell tumors [22].

Metastases and PitNET

10.7% of pituitary metastases in the German Registry of Pituitary Tumors are coexistent with a PitNET. The first two cases of this coexistence were published in 1985 [23].

In 2009 Hoellig et al. reviewed 15 cases with a metastasis inside a PitNET in already published literature and own cases. The study only included cases with metastases in the PitNET. They supposed that the metastasis follows the blood supply of the PitNET [24].

A further theory of pathogenesis assumes that the primary tumor initially metastasizes to the surrounding bone and is presumably vascularized to the pituitary gland. With a pre-existing PitNET, the primary tumor is more likely to metastasize into the PitNET. In 58% of our cases the primary tumor metastasized within the PitNET. In bioptical specimens this rate is 100%. The reason for this is presumably the changed formations of capillaries inside the PitNET. In addition, it is assumed that the tissue around the PitNET has a certain resistance due to the pre-existing lesion [25].

This theory is supported by the fact that breast, prostate, kidney, and lung cancers often metastasize to the bone and from there to the pituitary gland [26; 27; 28]. Metastases of these primary tumors were also identified in our study.

To further support this theory, biopsies of the surrounding bone could be helpful. However, the clinical relevance is uncertain due to the reduced life expectancy during a metastasizing cancer disease.

Cysts and PitNET

In unselected autopsy material, Rathke's cleft cysts occur in up to 33% of pituitaries [29]. The coexistence of Rathke's cleft cysts and PitNETs is rarely described in relation to this high incidence [4].

In our database 16.6% of all Rathke's cleft cysts in the tumor registry are associated with an PitNET. At the same time only 0.64% of all PitNETs are associated with a Rathke's cleft cyst. Noh et al. reported a comparable incidence of 0.51% in their study [30]. Sumida et al. even detected that 3.5% of all PitNETs are associated with Rathke's cleft cyst but the comparability to our studies is limited, because only radiological data were considered [31].

As the embryological origin of the anterior pituitary lobe and a Rathke's cleft cyst is the Rathke pouch, a combined origin can be assumed [32]. In further research, the cases with a Rathke's cleft cyst within the PitNET may be of interest to determine whether the two lesions have a common origin (proportion in our collective: 5.5%).

The combination of a colloid cyst and a PitNET has not yet been described to the best of our knowledge. In our study, 7.6% of the colloid cysts in the tumor registry were present adjacent to a PitNET.

The pathogenesis of colloid cysts is not fully clarified. It is assumed that colloid cysts arise by natural cell death. Afterwards small cysts arise around this area [33]. The coexistence with a PitNET is believed to be a fortuitous event.

Arachnoid cysts are very rare lesions that only make up 0.13% of the tumor registry. A coexistent PitNET was present in 9.5% of these cases. Pathogenetically, it is assumed that the mesencephalomechane often has a perforation [34], whereby a second lesion (such as a PitNET) can represent a valve on this membrane [35]. By dividing the arachnoid leaves, a cyst can arise from a roof of the diencephalon membrane and the base of the mesencephalomechane. With this theory the interacting coexistence of an arachnoid cyst and a PitNET can be explained.

Meningioma and PitNET

4% of sellar meningiomas in the tumor registry are in coexistence to a PitNET. In comparable studies on coexisting lesions of PitNETs and meningiomas it was found that GH secreting PitNETs are most frequently present in coexistence with meningiomas (30%) [36; 37].

Therefore, probably growth factors of the PitNET enhance meningioma development [37; 38]. Friend et al. stated in 1999 that GH and IGF-1 significantly increase the growth rate of meningiomas [38]. In our study no PitNET preference is present.

Further we only considered the cases in which the meningioma had a sellar location. But the study by Zhu et al. also shows that meningiomas, as primarily cranial tumors, do not require a close positional relationship to the PitNET to a suspect coherent pathogenetic relationship as the incidence of

meningiomas in the normal population (6/100,000) was significantly lower in this study than in patients with a preexisting PitNET (7/1000).

Primary inflammation and PitNET

Primary inflammation of the pituitary in addition to PitNETs is rarely described in the literature. Metastudies of Sivakoti et al. [39] identified nine cases of primary inflammation combined with a PitNET. In four cases the inflammation was granulomatous and in five cases lymphocytic.

14 PitNETs with primary inflammation were listed in the tumor registry. 64.3% of these were lymphocytic and 21.4% were granulomatous inflammation types.

In our study nine cases of primary hypophysitis were lymphocytic and three cases granulomatous.

In 1983, Holck et al. were the first to propose different theories for the coexistence of a PitNET and inflammation [40]. They assumed a random coincidence, but also that the PitNET could trigger the inflammation by producing specific substances. Similar hypotheses are published by others [39; 41]. Yamamoto et al. stated that the transcription factor PIT-1 is associated with hypophysitis [42]. Since 50% of our cases were associated with PIT-1-positive PitNETs, a link may be possible. In the study of Sivakoti et al. one third of coexisting PitNETs were PIT-1 positive [39].

From our studies we can conclude that it is important to consider possible tumorous double lesions during surgeries and in preoperative X-ray analyses. This is especially important in patients that show more complex anatomical locations of the lesions.

Declarations

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Conflict of interests

The authors declare that a conflict of interests does not exist.

Author's contributions

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D.K. Lüdecke: Surgery of patients, clinic
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M. Glatzel: Histopathology, immunocytochemistry
W.Saeger: Histopathology, immunocytochemistry, conception, discussion

Ethics

Do to the character (case report) of the manuscript an approval on ethics appears to be not necessary.

References

1. W. Saeger, D.K. Ludecke, M. Buchfelder, R. Fahlbusch, H.J. Quabbe, S. Petersenn, Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. *Eur. J. Endocrinol.* **156**, 203–216 (2007)
2. R.Y. Osamura, M.B.S. Lopes, A. Grossmann, G. Kontogeorgos, J. Trouillas, WHO classification of tumours of the pituitary, in *WHO Classification of Tumours of Endocrine Organs*, ed. by R.V. Lloyd, R.Y. Osamura, G. Klöppel, J. Rosai (International Agency for Research on Cancer, Lyon, 2017), pp. 11–63
3. O. Mete, M.B. Lopes, Overview of the 2017 WHO Classification of Pituitary Tumors. *Endocr Pathol* **28**, 228–243 (2017)
4. M. Koutourousiou, G. Kontogeorgos, P. Wesseling, A.J. Grotenhuis, A. Seretis, Collision sellar lesions: experience with eight cases and review of the literature. *Pituitary* **13**, 8–17 (2010)
5. S. Ezzat, S.L. Asa, W.T. Couldwell, C.E. Barr, W.E. Dodge, M.L. Vance, I.E. McCutcheon, The prevalence of pituitary adenomas: a systematic review. *Cancer* **101**, 613–619 (2004)
6. H. Buurman, W. Saeger, Subclinical adenomas in postmortem pituitaries: classification and correlations to clinical data. *Eur. J. Endocrinol.* **154**, 753–758 (2006)
7. G. Kontogeorgos, B.W. Scheithauer, E. Horvath, K. Kovacs, R.V. Lloyd, H.S. Smyth, D. Rologis, Double adenomas of the pituitary: a clinicopathological study of 11 tumors. *Neurosurgery* **31**, 840–849

(1992); discussion 849

8. T. Sano, H. Horiguchi, B. Xu, C. Li, A. Hino, M. Sakaki, S. Kannuki, S. Yamada, Double pituitary adenomas: six surgical cases. *Pituitary* **1**, 243–250 (1999)
9. O. Mete, O.M. Alshaikh, A. Cintosun, S. Ezzat, S.L. Asa, Synchronous Multiple Pituitary Neuroendocrine Tumors of Different Cell Lineages. *Endocr Pathol* **29**, 332–338 (2018)
10. G. Kontogeorgos, K. Kovacs, E. Horvath, B.W. Scheithauer, Multiple adenomas of the human pituitary. A retrospective autopsy study with clinical implications. *J. Neurosurg.* **74**, 243–247 (1991)
11. G. Zielinski, E.A. Sajjad, M. Maksymowicz, M. Pekul, A. Koziarski, Double pituitary adenomas in a large surgical series. *Pituitary* **22**, 620–632 (2019)
12. E. Ogando-Rivas, A.F. Alalade, J. Boatey, T.H. Schwartz, Double pituitary adenomas are most commonly associated with GH- and ACTH-secreting tumors: systematic review of the literature. *Pituitary* **20**, 702–708 (2017)
13. J.K. Ratliff, E.H. Oldfield, Multiple pituitary adenomas in Cushing's disease. *J. Neurosurg.* **93**, 753–761 (2000)
14. B. Yang, C. Yang, Y. Sun, J. Du, P. Liu, G. Jia, W. Jia, Y. Zhang, J. Wang, Y. Xu, S. Wang, Mixed gangliocytoma-pituitary adenoma in the sellar region: a large-scale single-center experience. *Acta Neurochir. (Wien)* **160**, 1989–1999 (2018)
15. M. Kurosaki, W. Saeger, D.K. Ludecke, Intracellular gangliocytomas associated with acromegaly. *Brain Tumor Pathol* **19**, 63–67 (2002)
16. G. Kontogeorgos, G. Mourouti, E. Kyrodinou, G. Liapi-Avgeri, E. Parasi, Ganglion cell containing pituitary adenomas: signs of neuronal differentiation in adenoma cells. *Acta Neuropathol* **112**, 21–28 (2006)
17. D. Voit, W. Saeger, D.K. Ludecke, Pituitary adenomas in acromegaly: Comparison of different adenoma types with clinical data. *Endocr Pathol* **10**, 123–135 (1999)
18. W. Saeger, M.J. Puchner, D.K. Ludecke, Combined sellar gangliocytoma and pituitary adenoma in acromegaly or Cushing's disease. A report of 3 cases. *Virchows Arch* **425**, 93–99 (1994)
19. S.L. Asa, K. Kovacs, G.T. Tindall, D.L. Barrow, E. Horvath, P. Vecsei, Cushing's disease associated with an intrasellar gangliocytoma producing corticotrophin-releasing factor. *Ann. Intern. Med.* **101**, 789–793 (1984)
20. L.J. Heng, D. Jia, L. Gong, W. Zhang, J. Ma, Y. Qu, Endoscopic Endonasal Resection of a Mixed Lesion of Gangliocytoma and Nonfunctioning Pituitary Adenoma. *World Neurosurg* **106** (2017) 1050 e1-1050 e6
21. M.C. Neidert, H. Leske, J.K. Burkhardt, S.S. Kollias, D. Capper, D. Schrimpf, L. Regli, E.J. Rushing, Synchronous pituitary adenoma and pituicytoma. *Hum Pathol* **47**, 138–143 (2016)
22. O. Mete, M.B. Lopes, S.L. Asa, Spindle cell oncocytomas and granular cell tumors of the pituitary are variants of pituicytoma. *Am. J. Surg. Pathol.* **37**, 1694–1699 (2013)

23. P.A. Molinatti, B.W. Scheithauer, R.V. Randall, E.R. Laws Jr., Metastasis to pituitary adenoma. *Arch Pathol Lab Med* **109**, 287–289 (1985)
24. A. Hoellig, P. Niehusmann, S. Flacke, R.A. Kristof, Metastasis to pituitary adenoma: case report and review of the literature. *Cent Eur Neurosurg* **70**, 149–153 (2009)
25. L.D.K. Saeger, W., Metastasen in der Hypophyse und der Sella. *Pathologe* **6**, 308–312 (1985)
26. Y.J. Niu, Y.T. Wen, W.W. Shen, L. Deng, L.L. Liu, H.L. Zhang, Risk factors for bone metastasis in patients with primary lung cancer: study protocol for a systematic review. *BMJ Open* **4**, e005202 (2014)
27. J.A. Sterling, J.R. Edwards, T.J. Martin, G.R. Mundy, Advances in the biology of bone metastasis: how the skeleton affects tumor behavior. *Bone* **48**, 6–15 (2011)
28. A. Javanbakht, M. D'Apuzzo, B. Badie, B. Salehian, Pituitary metastasis: a rare condition. *Endocr Connect* (2018)
29. W. el-Mahdy, M. Powell, Transsphenoidal management of 28 symptomatic Rathke's cleft cysts, with special reference to visual and hormonal recovery. *Neurosurgery* **42**, 7–16 (1998); discussion 16 – 7
30. S.J. Noh, J.Y. Ahn, K.S. Lee, S.H. Kim, Pituitary adenoma and concomitant Rathke's cleft cyst. *Acta Neurochir. (Wien)* **149**, 1223–1228 (2007)
31. M. Sumida, K. Migita, A. Tominaga, K. Iida, K. Kurisu, Concomitant pituitary adenoma and Rathke's cleft cyst. *Neuroradiology* **43**, 755–759 (2001)
32. M.J. Harrison, S. Morgello, K.D. Post, Epithelial cystic lesions of the sellar and parasellar region: a continuum of ectodermal derivatives? *J Neurosurg* **80**, 1018–1025 (1994)
33. G. Zielinski, J.K. Podgorski, J. Siwik, A. Warczynska, and W. Zgliczynski, [Colloid cysts of the pituitary gland]. *Neurol. Neurochir. Pol.* **36**, 293–306 (2002)
34. M. Miyajima, H. Arai, O. Okuda, M. Hishii, H. Nakanishi, K. Sato, Possible origin of suprasellar arachnoid cysts: neuroimaging and neurosurgical observations in nine cases. *J. Neurosurg.* **93**, 62–67 (2000)
35. M. Hasegawa, T. Yamashima, J. Yamashita, E. Kuroda, Symptomatic intrasellar arachnoid cyst: case report. *Surg Neurol* **35**, 355–359 (1991)
36. F. de Vries, D.J. Lobatto, A.H. Zamanipoor Najafabadi, M.C. Kleijwegt, M.J.T. Verstegen, P.J. Schutte, N.R. Biermasz, W.R. van Furth, Unexpected concomitant pituitary adenoma and suprasellar meningioma: a case report and review of the literature. *Br J Neurosurg* (2019) 1–5
37. A. Amirjamshidi, S.A. Mortazavi, M. Shirani, S. Saeedinia, H. Hanif, 'Coexisting pituitary adenoma and suprasellar meningioma-a coincidence or causation effect: report of two cases and review of the literature'. *J Surg Case Rep* **2017**, rjx039 (2017)
38. K.E. Friend, R. Radinsky, I.E. McCutcheon, Growth hormone receptor expression and function in meningiomas: effect of a specific receptor antagonist. *J. Neurosurg.* **91**, 93–99 (1999)
39. S. Sivakoti, B.N. Nandeesh, A.S. Bhatt, B.A. Chandramouli, Pituitary Adenoma with Granulomatous Hypophysitis: A Rare Coexistence. *Indian J Endocrinol Metab* **23**, 498–500 (2019)

40. S. Holck, H. Laursen, Prolactinoma coexistent with granulomatous hypophysitis. *Acta Neuropathol* **61**, 253–257 (1983)
41. S. Mitra, H. Chakraborty, Intratumoral granulomatous reaction in recurrent pituitary adenoma: A unique presentation. *J. Cancer Res. Ther.* **13**, 580–582 (2017)
42. M. Yamamoto, G. Iguchi, H. Bando, K. Kanie, R. Hidaka-Takeno, H. Fukuoka, Y. Takahashi, Autoimmune Pituitary Disease: New Concepts With Clinical Implications. *Endocr Rev* **41** (2020)

Figures

Figure 1

sparsely granulated GH PitNET and GHRH gangliocytoma GHRH gangliocytoma (right) with loosely positioned ganglionic cells (deep brown) together with an GH-secreting PitNET (left), blurred from the gangliocytoma; GHRH; 440: 1

Figure 2

Poorly differentiated bronchopulmonary adenocarcinoma with gonadotropic adenoma Large metastatic tumor within a densely granulated GH PitNET present only in very small remnants of PitNET cells (deep brown); GH; 500:1