Medicinska istaživanja 2023; 56(1):67-77 | DOI: 10.5937/medi55-41787

OPEN ACCESS

Medical Research | Published by Faculty of Medicine University of Belgrade

REVIEW

Pathology of sellar tumors: a contemporary diagnostic approach

Emilija Manojlović Gačić[1], Martina Bosić[1], Ivan Zaletel[2], Marko Stojanović[3,4], Mirjana Doknić[3,4], Sandra Pekić Đurđević[3,4], Dragana Miljić[3,4], Dejan Rašić[4,5], Sofija Glumac[1]

[1]Institute of Pathology, University of Belgrade, Faculty of Medicine, Belgrade, Serbia

[2]Institute of Histology, University of Belgrade, Faculty of Medicine, Belgrade, Serbia

[3]Neuroendocrine Department, Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Center of Serbia, Belgrade, Serbia

[4]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

[5]Clinic for Ophthalmology, University Clinical Center of Serbia, Belgrade, Serbia

Recived: 15 December 2022

Revised: 22 January 2023

Accepted: 25 February 2023

Check for updates

Funding information:
The authors received support from the Ministry of Education and Science of the Republic of Serbia (grant number 200110) and the Science Fund of the Republic of Serbia.

Competing interests:
The authors have declared that no competing interests exist

Correspondence to:
Emilija Manojlović Gačić, Institute of Pathology, University of Belgrade, Faculty of Medicine,
1, Dr Subotića Street, Belgrade, Serbia,
emilija.manojlovic-gacic@med.bg.ac.rs
emanojlovicgacic@gmail.com
Phone: +381 11 364 34 26

Summary

The sellar region is a complex area situated in the middle of the cranial base, with the pituitary gland in central position and anatomically close to the crossroads of vital structures, which makes the basis for the development of numerous endocrinological and neurological conditions caused by the expansion or secretory activity of the tumor tissue. In this article, we will summarize the literature enclosing histopathological and immunohistochemical aspects of sellar tumors, together with clinical characteristics, being the key elements in making a proper diagnosis. A histopathological diagnostic algorithm will be presented for the most frequent tumors of this region, pituitary neuroendocrine tumors, as well as tumors of the posterior pituitary, meningiomas, craniopharyngiomas, chordomas, germ cell tumors hematological malignancies, Rathke cleft cyst and metastases. Contemporary histopathological diagnostic approach to sellar tumors strongly depends on the routine use of immunohistochemistry for a broad spectrum of antibodies, as well as a detailed correlation with endocrinological, neurological, neurosurgical and neuroradiological aspects, which are mandatory for establishing an accurate diagnosis, reducing dilemmas, and offering the best options for further treatment of patients with sellar tumors.

Key words: sellar tumor, pituitary neuroendocrine tumor, immunohistochemistry

Cite this article as: Manojlović Gačić E, Bosić M, Zaletel I, Stojanović M, Doknić M, Pekić Đurđević S, Miljić D, Rašić D, Glumac S. Pathology of sellar tumors: a contemporary diagnostic approach Medicinska istraživanja 2023; 56(1):67-77 10.5937/medi55-41787

INTRODUCTION

The sellar region is a complex area located in the middle of the cranial base, with the pituitary gland in central position and anatomically closely connected with the crossroads of vital structures, including cavernous sinuses, sphenoid sinus and optic chiasm. The superposition of important endocrinological, neural and vascular structures of the sellar area represents the basis for the generation of numerous endocrinological and neurological conditions caused by the expansion of tumor tissue. Their type and severity depend on endocrinological activity, size, location, propagation, and biological behavior (1,2).

The most frequent neoplasms in the sellar region are pituitary neuroendocrine tumors (PitNETs), comprising up to 90% of neoplasms in this region (3). The remaining 9% are rare neoplasms originating from different cells and grades of malignancy. The heterogeneity of sellar tumors requires the use of several WHO classifications of tumors, presumably the classification of tumors of endocrine organs (4), followed by the classification of tumors of the central nervous system (5) and the classification of tumors of bone and soft tissues (6). Contemporary histopathological diagnostic approach to sellar tumors strongly depends on a routine use of immunohistochemistry for a broad spectrum of antibodies, as well as a detailed correlation with endocrinological, neurological, neurosurgical and neuroradiological aspects.

In this article, we will summarize the literature enclosing histopathological and immunohistochemical aspects of sellar tumors, together with clinical characteristics, being the key elements in making a proper diagnosis.

Pituitary neuroendocrine tumor (PitNET)

Pituitary neuroendocrine tumors, previously named pituitary adenomas (7), are the most frequent primary tumors of the pituitary gland (3). A contemporary diagnostic approach for PitNETs relies on the application of immunohistochemistry and the correlation of its results with clinical data (functioning vs non-functioning PitNET, the size and invasiveness of the tumor) (4). The diagnostic immunohistochemical panel consists of antibodies against anterior pituitary transcription factors – steroidogenic factor-1 (SF1), pituitary-specific transcription factor 1 (PIT1) and T-box family member TBX19 (TPIT), followed by antibodies against anterior pituitary hormones: growth hormone (GH), prolactin (PRL), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH) and adrenocorticotropic hormone (ACTH). The use of the antibody against low molecular weight cytokeratin (LMWCK) is not mandatory; it is of great importance for the recognition of granulation patterns of somatotroph tumors (4,8). PitNETs are classified according to their lineage of differentiation as follows:

1. PIT1-lineage PitNETs
   - Somatotroph tumors
     - Densely granulated somatotroph tumor
     - Sparsely granulated somatotroph tumor
   - Lactotroph tumors
     - Sparsely granulated lactotroph tumor
     - Densely granulated lactotroph tumor
   - Mammosomatotroph tumors
   - Thyrotroph tumors
   - Mature plurihormonal PIT1-lineage tumors
   - Immature PIT1-lineage tumors
   - Acidophil stem-cell tumor
   - Mixed somatotroph and lactotroph tumor
2. SF1-lineage PitNETs
   - Gonadotroph tumor
3. TPIT-lineage PitNETs
   - Corticotroph tumors
     - Densely granulated corticotroph tumor
     - Sparsely granulated corticotroph tumor
     - Crooke cell tumor
4. PitNETs with no distinct cell lineage
   - Null-cell tumor
   - Plurihormonal tumor (4,8)

The group of PIT1-lineage PitNETs is the most complex one, with numerous sub-categories whose precise diagnosis is of great importance since some of them (i.e., sparsely granulated somatotroph tumor, mature plurihormonal PIT1-lineage tumors and immature plurihormonal PIT1-lineage tumors) frequently show aggressive biological behavior and need a detailed and frequent follow-up.

Somatotroph tumors are most frequently functional, causing acromegaly. They are sub-classified according to their granulation pattern into densely and sparsely granulated somatotroph tumors. *Densely granulated somatotroph tumors* are characterized by diffuse and intensive PIT1 and GH positivity. The granulation pattern of densely granulated PitNETs is characterized by perinuclear or diffuse LMWCK cytoplasmic positivity **(Figure 1, A-D)**. *Sparsely granulated somatotroph tumors* are defined by diffuse and intensive PIT1 positivity which is surprisingly accompanied by focal, sparse (sometimes even negative) GH staining. The granulation pattern of sparsely granulated somatotroph tumors is defined by the presence of LMWCK positive, sharply demarcated, dot-like perinuclear staining, known as "fibrous bodies" in more than 70% of tumor cells **(Figure 1, E-H)** (4,8). Sparsely granulated somatotroph tumors demand special attention of endocrinologists and surgeons since they frequently show aggressive biological behavior and resistance to somatostatin analogues therapy (9). This can be at least partially explained by the absence of GNAS mutation and the lack of the activation of tumor senescence, both being present in densely granulated somatotroph PitNETs (10,11).

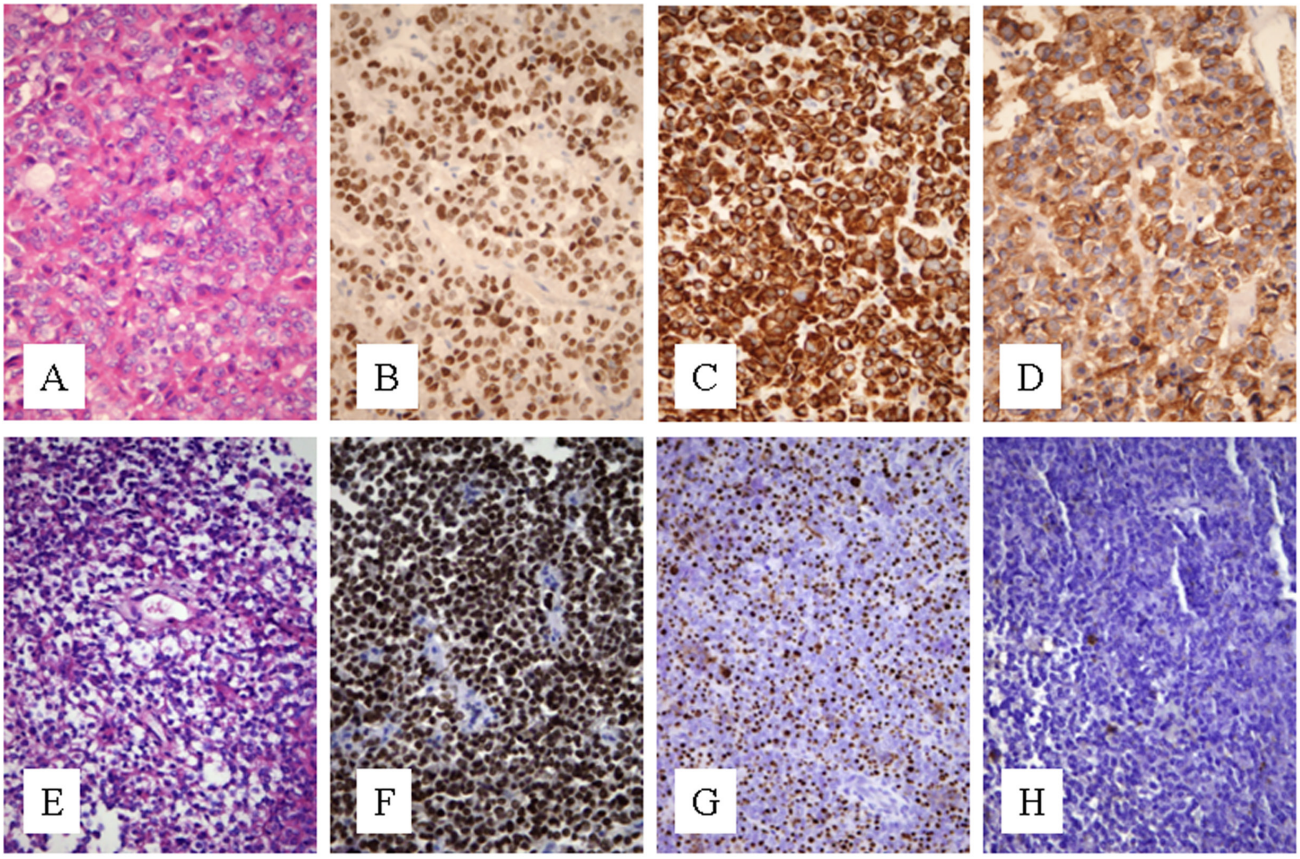

Figure 1. Somatotroph PitNETs. **A.** Densely granulated somatotroph PitNETs are typically acidophilic tumors (HE, x400); **B.** PIT1 nuclear positivity delineates somatotroph differentiation (PIT1, x400); **C.** CK8/18 positivity in densely granulated somatotroph PitNETs is diffuse cytoplasmic (CK8/18, x400); **D.** Densely granulated somatotroph PitNETs typically show diffuse and intensive GH positivity (GH, x400); **E.** Sparsely granulated somatotroph PitNETs are chromophobe tumors (HE, x400), **F.** PIT1 nuclear positivity is typically diffuse and intensive in sparsely granulated somatotroph PitNETs (PIT1, x400); **G.** Numerous spheric, CK8/18 positive perinuclear inclusions, named "fibrous bodies", are diagnostic hallmark of sparsely granulated somatotroph PitNETs (CK8/18, X400) **H.** GH positivity in sparsely granulated somatotroph PitNETs can be sparse, sometimes in scattered single cells (GH, x400).

Lactotroph tumors are the most frequent tumors of the anterior pituitary and they cause hyperprolactinemia. Intriguingly, they are extremely rare in surgical series owing to a very successful treatment with dopamine agonists (12). Currently, surgical treatment of prolactinomas is performed in rare cases resistant to dopamine agonists therapy (13). All lactotroph tumors are positive for PIT1 and estrogen receptor (ER). Their granulation pattern is defined according to the pattern of PRL positivity. *Sparsely granulated lactotroph tumors* are identified by PRL positivity in the Golgi zone, as opposed to rare *densely granulated lactotroph tumors* showing diffuse cytoplasmic PRL positivity (4,8). A great majority of surgically treated lactotroph tumors have previously been treated by dopamine agonists, which cause secondary changes in the tumor tissue including hyalinization, rarefaction of tumor cells, and scant PRL positivity. This is of great importance in cases with a small amount of tumor tissue provided for pathological analysis, since the majority of it can be seen as hyalinized tissue; tumor cells could be scattered and difficult to recognize (4,8). Lactotroph PitNETs in men need exceptional clinical attention due to their propensity for aggressive biological behavior (14).

Mammosomatotroph tumours are relatively rare tumors, most frequently presenting with acromegaly associated with hyperprolactinemia. Besides their PIT1 positivity, they are designated by diffuse GH positivity (similar to densely granulated somatotroph tumors) as well as positivity for PRL and ER (15). They have been presented as a distinct tumor type for the first time in the recent WHO classification (8).

Thyrotroph tumors are traditionally described as very rare tumors consisting of polygonal or spindle cells positive for PIT1 and TSH, causing central hyperthyroidism (16). Owing to a progress in understanding pituitary tumors, we can contemplate a majority of previously diagnosed "TSH-omas" could be currently re-diagnosed as mature and immature PIT1-lineage tumors, due to their frequent clinical presentation including the association of acromegaly and hyperthyroidism (8).

Mature plurihormonal PIT1-lineage tumors and immature PIT1-lineage tumors are recently recognized as new diagnostic categories (8,17), previously being designated as Silent subtype 3 pituitary adenomas (18). They are characterized by a wide spectrum of clinical presentations, ranging from non-functioning tumors to hyperthyroidism, acromegaly or galactorrhea and amenorrhea

(17). Morphologically, mature plurihormonal PIT1-lineage tumors are characterized by acidophilic tumor cells in diffuse arrangement, in contrast to the immature type, characterized by polygonal or spindle-shaped cells resembling thyrotrophs. The only consistent immunohistochemical finding in this exceptional type of PitNET is diffuse and intensive PIT1 positivity. In mature forms, GH, PRL and TSH positivity are frequently observed, in contrast to immature forms, where the percentage of GH, PRL and TSH cells decreases to scattered cells. Although very rare, immature PIT1-lineage tumors demand clinical attention and close follow-up due to the predisposition for aggressive biological behavior (8).

Acidophil stem-cell tumor is an extremely rare type of tumor belonging to the PIT1 lineage. It is an example of tumor composed of precursor cells, like immature plurihormonal PIT1-lineage tumors. They are usually large tumors with hyperprolactinemia which is of a lower level than expected for tumor size. Similarly, with mammosomatotroph tumors, acidophil stem-cell tumor has been presented as a distinct tumor type for the first time in the WHO classification 2022, previously being presented as a subtype of lactotroph tumor. This type of PitNET has unique morphological findings: "giant mitochondria" that can be observed on HE staining as intracytoplasmic vacuole. In immunohistochemistry, acidophil stem-cell tumor is diffusely positive for PIT1, ER and PRL and focally for GH (8).

Mixed somatotroph and lactotroph tumors are composed of two distinct populations of tumor cells; most frequently densely granulated somatotrophs and sparsely granulated lactotrophs (10).

SF1-lineage PitNETs, presented as a single category of gonadotroph tumors, are most frequent in surgical series. Since they are typically non-functioning tumors, their clinical presentation is caused by their compression to cavernous sinuses, optic chiasm, and meninges, causing headaches and visual impairment (19). The introduction of antibodies against anterior pituitary transcription factors caused a significant increase in the number of diagnosed gonadotroph tumors, since a great majority of them have been incorrectly diagnosed as null-cell adenomas, due to the lack of the positive stain for FSH and/or LH (20). The FSH and LH positivity is typically focal when present (4,10).

TPIT-lineage PitNETs include three types of PitNETs, two of them being PitNETs with aggressive biolog-

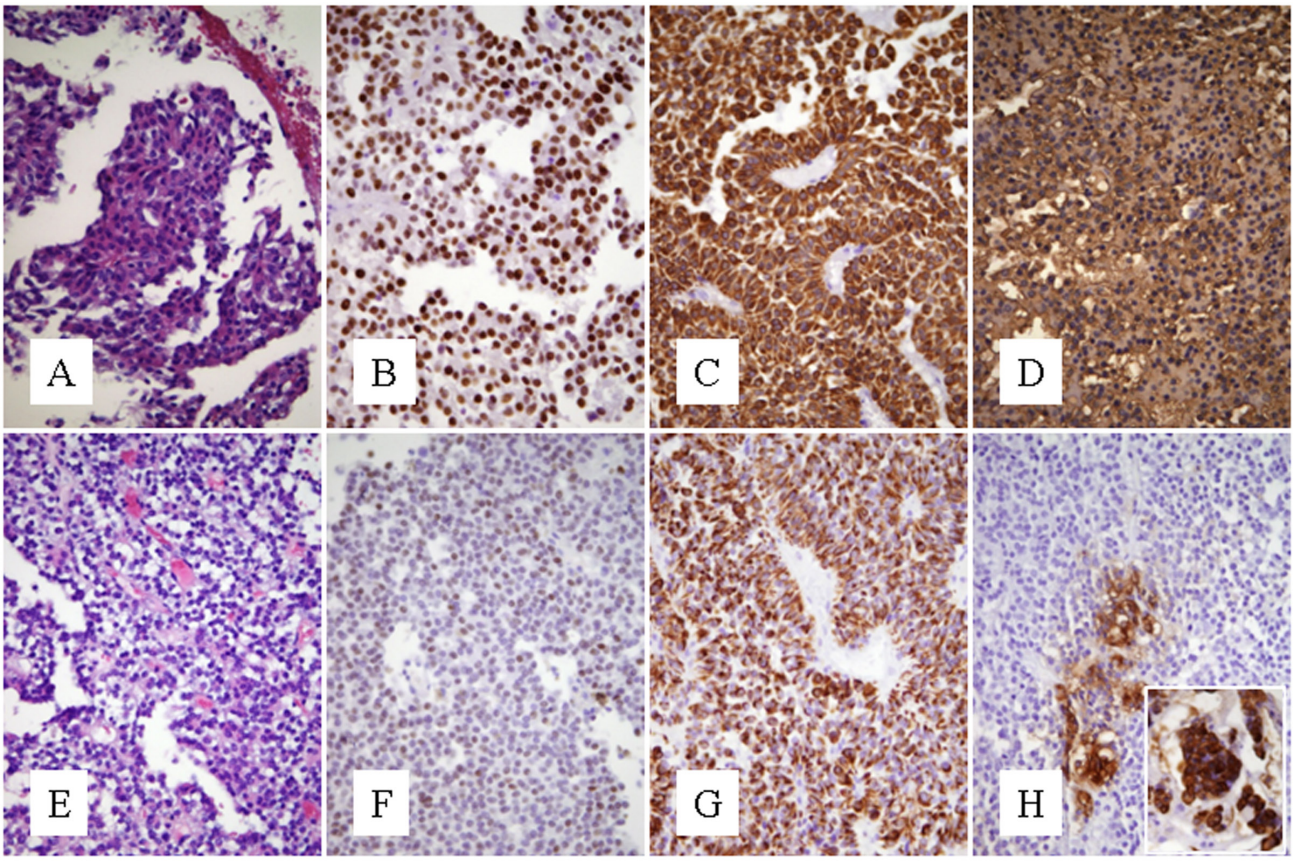

Figure 2. Corticotroph PitNETs **A.** Densely granulated corticotroph PitNETs are basophil tumours on HE stain (HE, x400); **B.** TPIT nuclear positivity is diffuse and intensive in densely granulated corticotroph PitNETs (TPIT, x400); **C.** CK8/18 positivity is typically diffuse and intensive in all corticotroph PitNETs, including densely granulated (CK8/18, x400); **D.** Diffuse and intensive ACTH positivity is the diagnostic hallmark of densely granulated corticotroph PitNETs (ACTH, x400); **E** Tumor cells of silent corticotroph PitNET are typically chromophobe (HE, x40); **F.** TPIT nuclear positivity is focal and of variable intensity in silent corticotroph PitNETs (TPIT, x400); **G.** CK8/18 positivity is typically diffuse and intensive in silent corticotroph PitNETs (CK8/18, x400); **H.** ACTH positivity is typically sparse, sometimes absent, being the diagnostic hallmark of sparsely granulated corticotroph PitNETs (ACTH, x400). Insert Crooke hyaline change in corticotroph cells, as a morphological proof of hypercortisolemia).

ical behavior. *Densely granulated corticotroph tumors* are typically of small size, around few millimeters in diameter, and cause florid Cushing disease (21). On HE slides, they are basophilic tumors, with diffuse and intensive TPIT, LMWCK and ACTH positivity **(Figure 2, A-D)**. Contrary to this, *sparsely granulated corticotroph tumors* are relatively large tumors, frequently invading surrounding structures, causing frequent recurrences (22), with variable Cushing disease (23). On HE slides present as chromophobe tumors, with variable immunohistochemical expression of TPIT and ACTH and diffuse LMWCK positivity. It is worth noting that ACTH positivity could be absent **(Figure 2, E-H)**. The number of diagnosed sparsely granulated corticotroph tumors increased after the introduction of the antibody against TPIT in routine practice. Until then, they were misdiagnosed as null-cell adenomas. Sparsely granulated corticotroph PitNETs frequently show aggressive biological behavior which is frequently linked with ATRX mutation (24). *Crooke cell tumor* is an extremely rare variant of corticotroph tumor composed of cells with Crookes hyaline change, morphological evidence of hypercortisolemia and hormonal feedback inhibition **(Figure 2, H, insert)**. The cytoplasm of Crooke cells is filled with a pale hyaline ring intensely reactive for LMWCK. ACTH-positive granules can be observed only at the periphery of the cell. The accurate diagnosis of this unique tumor is of great importance since they show aggressive biological behavior (8).

PitNETs with no distinct cell lineage are very rare in the era of routine use of antibodies for anterior pituitary transcription factors. The number of diagnosed null-cell tumors, characterized by the lack of expression of any anterior pituitary hormone and transcription factor, significantly decreased after the introduction of the use of antibodies for anterior pituitary transcription factors (25). A great majority of ex-null-cell adenomas became re-diagnosed as gonadotroph tumors (owing to SF1 positivity); a smaller part of ex-null-cell adenomas with aggressive biological behavior was re-diagnosed as silent corticotroph tumors, owing to TPIT positivity (26). Contemporary diagnosis of null-cell tumor, besides negative immunohistochemical stains for all anterior pituitary hormones and transcription factors, requires the exclusion of the possibility of metastases of neuroendocrine tumors from other sites (25), or the diagnostic use of proteomics (27,28). Plurihormonal tumors are also exceedingly rare. By definition, they are composed of tumor cells with multiple cell lineages. The crucial step in the diagnosis of plurihormonal tumor is the exclusion of the possibility of cross-reactions of antibodies for anterior pituitary hormones and transcription factors, as well as reassessment of the quality of the immunohistochemistry (29).

Contemporary molecular diagnostics is not needed in routine diagnostics of PitNETs, since proteomics analyses follow the classification tree established by immunohistochemistry (27,28). The molecular diagnostic approach could be of great importance in rare sellar tumors without detectable lineage of differentiation by immunohistochemistry (25). Namely, some rare forms of PitNETs produce anterior pituitary transcription factors in such low amounts that they could be detected (and subsequently diagnosed and classified) only by proteomics (27,28).

Tumors of the posterior pituitary

Modern understanding of posterior pituitary tumors is that they represent a spectrum of low-grade tumor types with a single common characteristic: thyroid transcription factor 1 (TTF1) positivity (30,31). Spindle-cell oncocytoma, pituicytoma and granular cell tumor of the sellar region originate from pituicytes of the posterior pituitary or infundibulum. Their differentiation relies on their morphological characteristics on HE slides since their immunohistochemical profile is very similar: they show strong positivity for Vimentin and S-100, whilst GFAP, EMA, CD56, CD68 and bcl-2 stains are variable. Pituicytomas are composed of bipolar spindle cells arranged in sheets and short fascicles. Granular cell tumors consist of polygonal cells with granular cytoplasm. Finally, spindle cell oncocytomas are, as the name implies, constituted of spindled or epithelioid tumor cells with brightly eosinophilic granular cytoplasm (5).

TTF1 positivity in a sellar tumor should be regarded with special attention and with numerous additional immunohistochemical staining, bearing in mind that TTF1 is widely present in lung and thyroid tumors, with a chance that the tumour is a metastasis from tumors of these organs.

Meningioma

Sellar and parasellar meningiomas represent 5-10% of intracranial meningiomas (32). Their clinical, endocrinological and radiological presentation resembles the most frequent sellar tumors PitNETs (33). Subsequently, histopathological examination is crucial for the diagnosis, which is sometimes challenging. The only immunohistochemical marker constantly expressed in all types of meningiomas, regardless of the grade, is SSTR2A. Furthermore, this is the only immunohistochemical marker mandatory for the diagnosis of meningioma according to the WHO criteria (5). It should be noted that neuroendocrine tumors also express SSTR2A and that a broader immunohistochemical panel should be used for the correct differential diagnosis. The meningothelial origin of tumor cells can be confirmed by positive immunohistochemical staining for EMA, Vimentin and PR. However, EMA and PR positivity is frequently lost with an increase in meningioma grade. Meningiomas are negative for GFAP, SOX-10, STAT6, Inhibin, Melan A and HMB45. S-100, cytokeratin AE1/AE3 and CD34 positivity are observed in rare cases (34). Bearing in mind the broad spectrum of differential diagnoses of sellar menin-

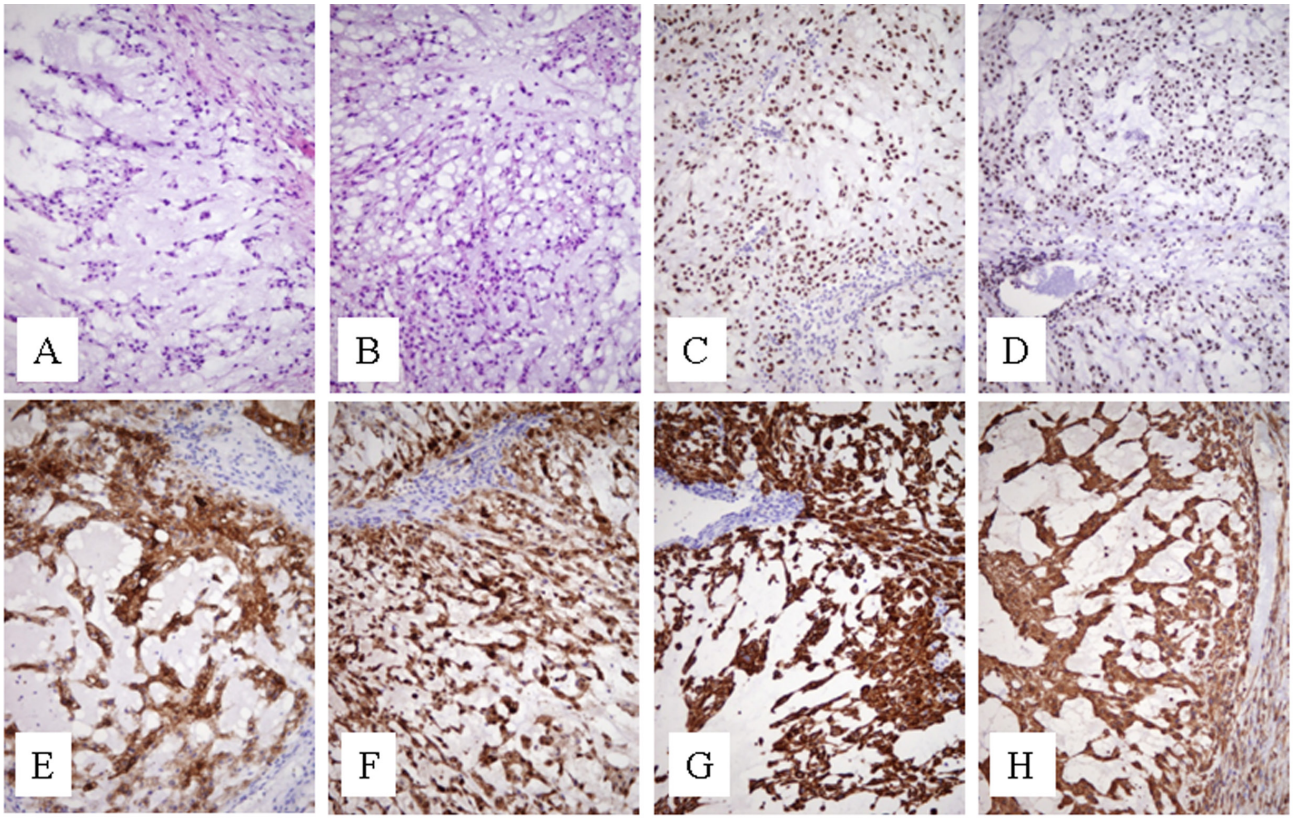

Figure 3. A. Chordomas are characterized by epithelioid cells organized in trabecules, separated by myxoid stroma (HE, x400). **B.** Chordoma cells sometimes have vacuolated cytoplasm, giving the appearance of "physaliphora cells" (HE, x400). **C.** Brachiury positivity is mandatory for diagnosing chordoma (Brachiury, x400); Chordomas are usually positive for EMA (**D.**, EMA, x400), S-100 (**E.**, S-100, x400); panCK (AE1/AE3) (**F.**, panCK (AE1/AE3), x400); INI1 (**G.**, INI1, x400) and Vimentin (**H.**, Vimentin, x400).

giomas, we recommend the use of a wider spectrum of immunohistochemical markers and clinical-pathological correlation for its reliable diagnosis.

Chordoma

Chordomas of the sellar region account for about 0.5% of all sellar masses (3). Nevertheless, they are not surprising lesions on this location since they are midline tumors. Although their histopathological appearance is unique, with lobular architecture, cords of epithelioid cells embedded in the extracellular myxoid matrix and "physaliphorous cells" **(Figure 3, A-B)** (6), immunohistochemistry is mandatory for the diagnosis. Brachiury is a mandatory marker for the reliable diagnosis of chordoma **(Figure 3C)**. It is worth noting that the patterns of expression of Brachiury are variable (35); therefore, additional markers are needed for the diagnosis, such as positivity for Vimentin, S-100, cytokeratins, EMA, INI1 **(Figure 3 D-H)**) and negative stains for vascular (CD34, CD31, ERG, FLI) and neuroendocrine (Synaptophysin, SSTR2A) markers (6).

Clinical and radiological correlation is helpful in cases where the material obtained for the histopathological diagnosis is scant since chordomas frequently affect clivus.

Craniopharyngioma

For decades, craniopharyngiomas have been classified as a tumor type with two subtypes, named adamantinomatous and papillary. The current WHO classification of CNS tumors classifies them as distinct tumor types, corresponding to CNS WHO grade 1 (5). Both types are clinically usually presented with hypopituitarism or signs of increased intracranial pressure (36).

Adamantinomatous craniopharyngiomas constitute all craniopharyngiomas diagnosed in childhood and up to 80% of craniopharyngiomas diagnosed in adults (5). They are composed of epithelium with peripheral palisading, organized in cords, lobules, nodular whorls and trabeculae. Nodules of anucleate ghost-like squamous cells, named "wet keratin", calcifications and areas of microcystic stellate reticulum are characteristic **(Figure 4 A-B)**. Furthermore, xanthogranulomatous reaction, cholesterol clefts, hemosiderin deposits and lymphoplasmacytic infiltrate can be observed as a reaction to the ruptured cystic material, making differential diagnosis with the cyst of Rathke cleft challenging (5). Nuclear p63 positivity is observed in all layers of the epithelium in adamantinomatous craniopharyngiomas **(Figure 4C)**. Nuclear translocation of ß-catenin positivity is seen in scattered cells **(Figure 4D)** (37).

Papillary craniopharyngiomas principally occurs in adults (5). They are composed of non-keratinizing epithelium covering papillary fibrovascular cores **(Figure 4 E-F)**. In contrast to adamantinomatous craniopharyngiomas, wet keratin, stellate reticulum, palisading of the cells and calcifications are absent. Squamous differentiation can be proved by p63 and CK5/6 positivity, whilst

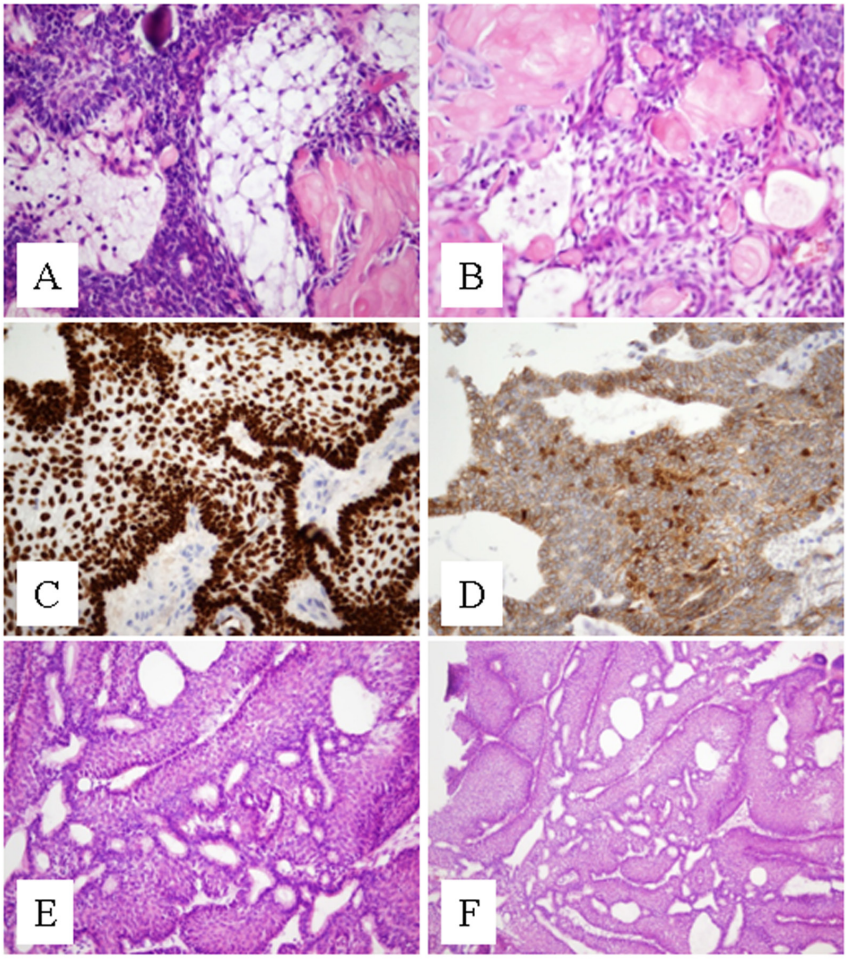

Figure 4. Adamantinomatous craniopharyngioma is composed of cords and trabeculae of cells punctuated by wet keratin (composed of anucleated ghost cells) and stellate reticulum (**A and B**, HE x400). P63 demarcates nuclei in all layers of epithelial cells adamantinomatous craniopharyngioma (**C,** p63, x400). **D.** β-catenin positivity is membranous in the majority of epithelial cells; nuclear translocation of positivity is observed in scattered cells (β-catenin, x400). **E.** Papillary craniopharyngioma is composed of well-differentiated non-keratinizing squamous epithelium (HE, x400); **F.** Papillary architecture can be observed on lower magnification (HE, x200).

ß-catenin positivity is membranous. All papillary craniopharyngiomas harbor BRAF V600E mutation, which can be detected by immunohistochemistry (37). This characteristic is useful in challenging cases of differentiation between papillary craniopharyngiomas and Rathke cleft cyst with squamous metaplasia.

Rathke cleft cyst

Rathke cleft cyst occurs at the junction between the anterior and posterior lobe of the pituitary gland, causing compressive effects on the gland and adjacent structures (38,39). The lining of the cyst varies from cuboidal to cylindric cells, with occasional ciliation on the surface. If present on slides, the content of the cyst is dense, colloidal and amorphous. In immunohistochemistry, the epithelium is positive for cytokeratins (usually CK7, exceedingly CK20) and negative for S-100 and Synaptophysin **(Figure 5)** (40). The differential diagnosis between Rathke cleft cysts and craniopharyngiomas might be challenging and demands a detailed correlation between pathological, endocrinological, neurosurgical and neuroradiological findings (41). Regarding papillary craniopharyngioma, it could be overcome by the use of BRAF V600E antibody, since its immunohistochemical positivity is observed in papillary craniopharyngioma, in contrast to the epithelium of Rathke cleft cyst, where it is negative (42).

Germ cell tumors

After the pineal region, the sellar localization of germinomas is the most frequent (5). They usually affect children, without sex predilection on the sellar region. The diagnosis of teratomas (mature, immature and the variant of somatic-type malignancy), germinomas, embryonal carcinomas, yolk-sac tumors, choriocarcinomas, as well as mixed germ cell tumors should be established with a specific combination of a broad spectrum of antibodies, including OCT4, CD117, PLAP, SALL4, CD30, AFP, ß-HCG and LMWCK for all cases of sellar tumors suspected to germ-cell tumors. Germinomas are characterized by OCT4, CD117, D2-40, PLAP and SALL4 positivity **(Figure 6)** (43). Embryonal carcinomas are positive for OCT4, PLAP, SALL4, CD30 and LMWCK. Yolk-sac tumors show positivity for SALL, AFP and variably for PLAP whilst choriocarcinomas are positive for ß-HCG, LMWCK and variably for PLAP (5). Importantly, all slides should be analyzed with special care, having in mind the possibility that some types of mixed germ cell tumors can be present in extremely small areas (sometimes a square millimeter). The presence of additional components of germ cell tumors prompts changes in oncological treatments of such patients.

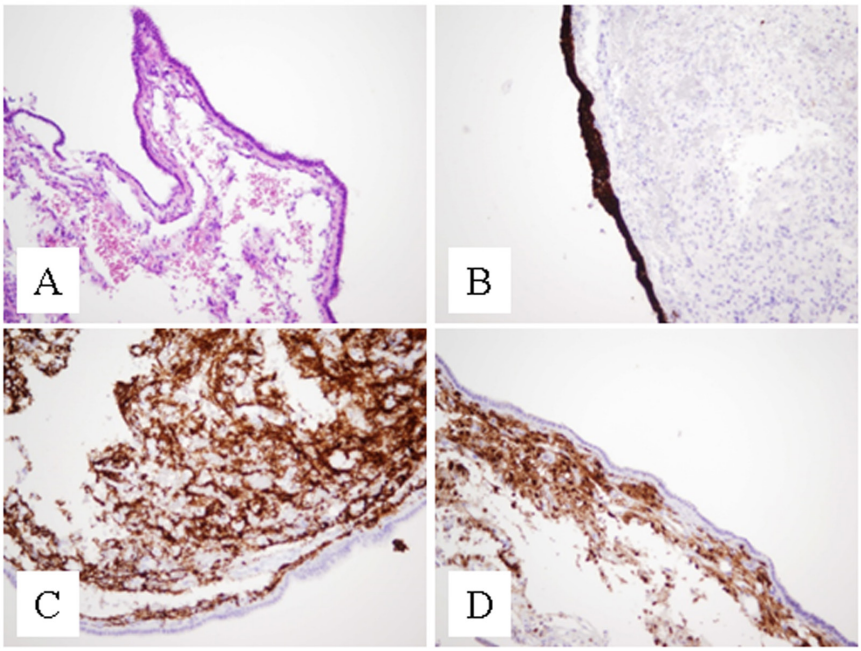

Figure 5. Rathke cleft cyst. **A.** The wall of the cyst is covered by cylindric epithelium (HE, x200). The epithelium is positive for CK7 **(B)** and negative for Synaptophysin (**C,** x200) and S-100 (**D**, x200). Synaptophysin demarcates adjacent anterior pituitary cells **(C)** whilst S-100 demarcates adjacent posterior pituitary cells **(D).**

Metastases

Metastases in the sellar region are rare, encompassing 0.4% of all intracranial metastases and 1.8% of surgically treated sellar lesions (3,44). They most frequently originate from the lungs and breast; metastases originating from the thyroid, cervix, kidney and digestive system were also observed (45). A broad spectrum of immunohistochemical markers (including CK7, CK20, TTF-1, PAX8, CDX2, GATA3) is mandatory for the recognition of the origin of metastasis **(Figure 7)**. This panel should be applied after the negative basic panel for pituitary gland tumors, as well as for all sellar tumors with an expression of neuroendocrine markers, keeping in mind that a metastasis could also come from neuroendocrine tumors of other localization (25). Positivity for TTF-1 and GATA3 should be considered with caution since posterior pituitary tumors express TTF1 and some PitNET types (thyrotroph PitNETs, mature plurihormonal PIT1-lineage tumors and immature PIT1-lineage tumor) express GATA3. These positive stains should be interpreted together with other anterior pituitary transcription factors and hormones.

Hematologic malignancies

Hematologic malignancies are rare in sellar region, mostly being detected in end-stage primary disease (3). Nevertheless, they should be considered as a primary

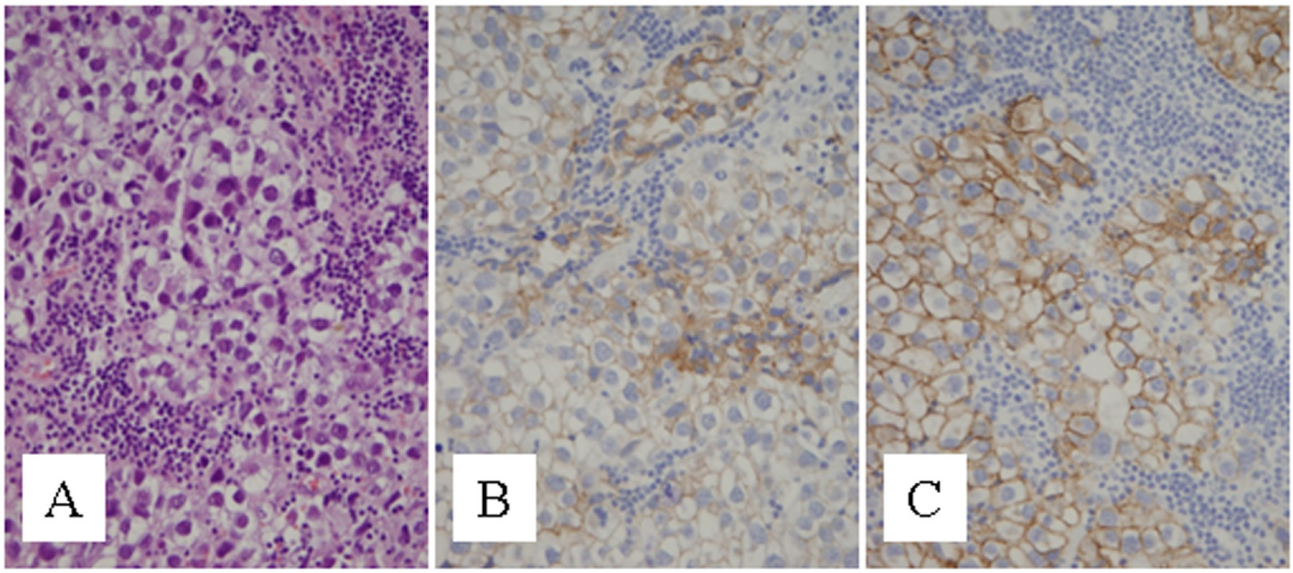

Figure 6. Germinoma. **A.** On HE sections, germinoma is characterized by large polygonal cells with pale cytoplasm, large nuclei with nucleoli, and separated with groups of small lymphocytes (HE, x400). **B.** Germinomas show CD117 positivity in membrane and/or Golgi zone (CD117, x400); **C.** Membranous D2-40 positivity is characteristic of germinoma (D2-40, x400).

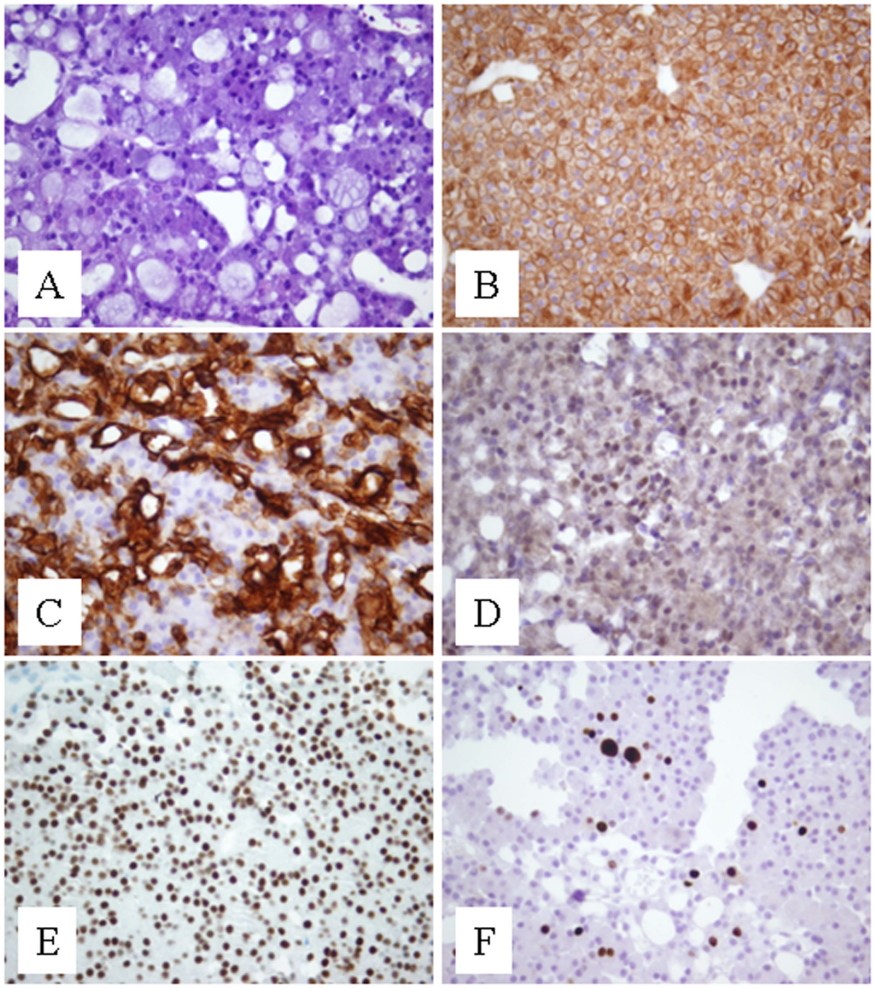

Figure 7. Metastasis of the carcinoma of the kidney in the sellar region is recognized by cribriform histological pattern (**A,** HE, x400), diffuse cytokeratin AE1/AE3 (**B,** x400) and focal cytokeratin 7 (**C,** x400) positivity. Focal nuclear positivity for GATA3 (**D,** x400) and diffuse nuclear PAX8 positivity (**E,** x400) suggest that the metastasis originates from renal carcinoma. Increased proliferative Ki-67 index, compared to other sellar tumors, also suggest the possibility of metastasis (**F,** x400).

manifestation of the disease, although being exceedingly rare. Multiple myeloma, lymphomas (both secondary and primary), as well as acute and chronic leukemia were described in literature (46). Such cases should be carefully distinguished from more frequent hypophysitis and correlated with endocrinological and hematologic findings before establishing the final diagnosis by an experienced hematopathologist (47). A large list of antibodies for hematologic malignancies and molecular analyses are necessary for the proper diagnosis, which overcomes the scope of this review.

Conclusion

We conclude that the heterogeneity of sellar tumors requires extensive experience, principally in the field of neuropathology, in order to cover a wide spectrum of histopathological diversity and avoid pitfalls in their diagnosis. A multidisciplinary approach, including endocrinological, neuroradiological and neurosurgical aspects, is mandatory for establishing an accurate diagnosis, reducing dilemmas and offering the best options for the further treatment of patients with sellar tumors.

Acknowledgements

None

Conflict of interest

None to declare

References

1. Manojlovic-Gacic E, Bollerslev J, Casar-Borota O. Invited Review: Pathology of pituitary neuroendocrine tumours: present status, modern diagnostic approach, controversies and future perspectives from a neuropathological and clinical standpoint. Neuropathol Appl Neurobiol. 2020;46:89-110. doi: 10.1111/nan.12568.
2. Manojlovic-Gacic E, Rostami E, Karavitaki N, Casar-Borota O. Histopathology of Parasellar Neoplasms. Neuroendocrinology 2020;110:740-752. doi: 10.1159/000507084.
3. Saeger W, Lüdecke DK, Buchfelder M, Fahlbusch R, Quabbe HJ, Petersenn S. Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. Eur J Endocrinol. 2007;156:203-16. doi: 10.1530/eje.1.02326.
4. WHO Classification of Tumours Editorial Board, Lloyd RV, Osamura RY, Kloppel G, Rosai J. WHO Classification of Tumours of Endocrine Organs. 4th ed. Lyon: International Agency for Research on Cancer; 2017.

5. WHO Classification of Tumours Editorial Board. World Health Organization Classification of Tumours of the Central Nervous System. 5th ed.Lyon: International Agency for Research on Cancer; 2021.
6. The WHO Classification of Tumours Editorial Board. World Health Organisation Classification of Tumours Soft Tissue and Bone Tumours, 5th ed. Lyon: International Agency for Research on Cancer; 2020.
7. Asa SL, Asioli S, Bozkurt S, Casar-Borota O, Chinezu L, Comunoglu N et al.Pituitary neuroendocrine tumors (PitNETs): nomenclature evolution, not clinical revolution. Pituitary 2020;23:322-325. doi: 10.1007/s11102-019-01015-0.
8. Asa SL, Mete O, Perry A, Osamura RY. Overview of the 2022 WHO Classification of Pituitary Tumors. Endocr Pathol. 2022;33:6-26. doi: 10.1007/s12022-022-09703-7.
9. Durmus ET, Atmaca A, Kefeli M, Çalışkan S, Mete O, Aslan K et al. Age, GH/IGF-1 levels, tumor volume, T2 hypointensity, and tumor subtype rather than proliferation and invasion are all reliable predictors of biochemical response to somatostatin analogue therapy in patients with acromegaly: A clinicopathological study. Growth Horm IGF Res. 2022; 67:101502. doi: 10.1016/j.ghir.2022.101502.
10. Asa SL, Ezzat S. An Update on Pituitary Neuroendocrine Tumors Leading to Acromegaly and Gigantism. J Clin Med. 2021;10:2254. doi: 10.3390/jcm10112254.
11. Manojlovic-Gacic E, Skender-Gazibara M, Popovic V, Soldatovic I, Boricic N, Raicevic S et al. Oncogene-Induced Senescence in Pituitary Adenomas--an Immunohistochemical Study. Endocr Pathol. 2016;27:1-11. doi: 10.1007/s12022-015-9405-4.
12. Karatas S, Hacioglu Y, Rakicioglu T. Prolactinoma - which patients react favorably to cabergoline medication? Endocr Regul. 2022;56:279-283. doi: 10.2478/enr-2022-0030.
13. Force BK, Staggers K, Sebastian S, Takashima M, Yoshor D, Samson SL. Endoscopic Endonasal Transsphenoidal Surgery for Patients with Prolactinomas: Indications and Outcomes. World Neurosurg. 2022; 19:S1878-8750(22)01459-0. doi: 10.1016/j.wneu.2022.10.043.
14. Trouillas J, Delgrange E, Wierinckx A, Vasiljevic A, Jouanneau E, Burman P et al. Clinical, Pathological, and Molecular Factors of Aggressiveness in Lactotroph Tumours. Neuroendocrinology 2019; 109:70-76. doi: 10.1159/000499382.
15. Lv L, Jiang Y, Yin S, Hu Y, Chen C, Ma W et al. Mammosomatotroph and mixed somatotroph-lactotroph adenoma in acromegaly: a retrospective study with long-term follow-up. Endocrine 2019; 66:310-318. doi: 10.1007/s12020-019-02029-1.
16. Luo P, Zhang L, Yang L, An Z, Tan H. Progress in the Pathogenesis, Diagnosis, and Treatment of TSH-Secreting Pituitary Neuroendocrine Tumor. Front Endocrinol (Lausanne) 2020;11:580264. doi: 10.3389/fendo.2020.580264.
17. Mete O, Gomez-Hernandez K, Kucharczyk W, Ridout R, Zadeh G, Gentili F et al. Silent subtype 3 pituitary adenomas are not always silent and represent poorly differentiated monomorphous plurihormonal Pit-1 lineage adenomas. Mod Pathol. 2016;29:131-42. doi: 10.1038/modpathol.2015.151.
18. De Lellis RA, Lloyd RV, Heitz PU, et al, 3rd ed. WHO Classification of Tumours, Pathology and Genetics of Tumours of Endocrine Organs. Lyon: IARC Press; 2004.
19. Manojlovic-Gacic E, Engström BE, Casar-Borota O. Histopathological classification of non-functioning pituitary neuroendocrine tumors. Pituitary. 2018;21:119-129. doi: 10.1007/s11102-017-0855-1.
20. Chatrath A, Kosyakovsky J, Patel P, Ahn J, Elsarrag M, Young LC et al. Impact of histopathological classification of non-functioning adenomas on long term outcomes: comparison of the 2004 and 2017 WHO classifications. Pituitary. 2022 doi: 10.1007/s11102-022-01281-5. Epub ahead of print.
21. Broersen LHA, Biermasz NR, van Furth WR, de Vries F, Verstegen MJT, Dekkers OM et al. Endoscopic vs. microscopic transsphenoidal surgery for Cushing's disease: a systematic review and meta-analysis. Pituitary 2018;21:524-534. doi: 10.1007/s11102-018-0893-3.
22. Fountas A, Lavrentaki A, Subramanian A, Toulis KA, Nirantharakumar K, Karavitaki N. Recurrence in silent corticotroph adenomas after primary treatment: A systematic review and meta-analysis. J Clin Endocrinol Metab. 2018. doi: 10.1210/jc.2018-01956. Epub ahead of print.
23. Andonegui-Elguera S, Silva-Román G, Peña-Martínez E, Taniguchi-Ponciano K, Vela-Patiño S, Remba-Shapiro I et al. The Genomic Landscape of Corticotroph Tumors: From Silent Adenomas to ACTH-Secreting Carcinomas. Int J Mol Sci. 2022;23:4861. doi: 10.3390/ijms23094861.
24. Casar-Borota O, Boldt HB, Engström BE, Andersen MS, Baussart B, Bengtsson D et al. Corticotroph Aggressive Pituitary Tumors and Carcinomas Frequently Harbor ATRX Mutations. J Clin Endocrinol Metab. 2021;106:1183-1194. doi: 10.1210/clinem/dgaa749.
25. Casar-Borota O, Botling J, Granberg D, Stigare J, Wikström J, Boldt HB et al. Serotonin, ATRX, and DAXX Expression in Pituitary Adenomas: Markers in the Differential Diagnosis of Neuroendocrine Tumors of the Sellar Region. Am J Surg Pathol. 2017;41:1238-1246. doi: 10.1097/PAS.0000000000000908.
26. Sjöstedt E, Bollerslev J, Mulder J, Lindskog C, Pontén F, Casar-Borota O. A specific antibody to detect transcription factor T-Pit: a reliable marker of corticotroph cell differentiation and a tool to improve the classification of pituitary neuroendocrine tumours. Acta Neuropathol. 2017;134:675-677. doi: 10.1007/s00401-017-1768-9.
27. Tebani A, Jotanovic J, Hekmati N, Sivertsson Å, Gudjonsson O, Edén Engström B et al. Annotation of pituitary neuroendocrine tumors with genome-wide expression analysis. Acta Neuropathol Commun. 2021;9:181. doi: 10.1186/s40478-021-01284-6.
28. Neou M, Villa C, Armignacco R, Jouinot A, Raffin-Sanson ML, Septier A et al. , Pangenomic Classification of Pituitary Neuroendocrine Tumors. Cancer Cell. 2020;37:123-134.e5. doi: 10.1016/j.ccell.2019.11.002.
29. Torlakovic EE, Cheung CC, D'Arrigo C, Dietel M, Francis GD, Gilks CB et al. From the International Society for Immunohistochemistry and Molecular Morphology (ISIMM) and International Quality Network for Pathology (IQN Path). Evolution of Quality Assurance for Clinical Immunohistochemistry in the Era of Precision Medicine. Part 3: Technical Validation of Immunohistochemistry (IHC) Assays in Clinical IHC Laboratories. Appl Immunohistochem Mol Morphol. 2017;25(3):151-159. doi: 10.1097/PAI.0000000000000470.
30. Qiao N, Cheng H, Zhang Z, Ye H, Shen M, Shou X et al. Recommendation to improve the WHO classification of posterior pituitary tumors as a unique entity: evidence from a large case series. Endocr Connect. 2022;11:e220188. doi: 10.1530/EC-22-0188.
31. Guerrero-Pérez F, Vidal N, Marengo AP, Pozo CD, Blanco C, Rivero-Celada D et al. Posterior pituitary tumours: the spectrum of a unique entity. A clinical and histological study of a large case series. Endocrine 2019;63:36-43. doi: 10.1007/s12020-018-1774-2.
32. Bang M, Suh JH, Park JB, Weon YC. Pure Intrasellar Meningioma Mimicking Pituitary Macroadenoma: Magnetic Resonance Imaging and Review of the Literature. World Neurosurg. 2016; 91:675.e1-4. doi: 10.1016/j.wneu.2016.04.063
33. Chen A, Xiang R, Zhou R. Pure Intrasellar Meningioma Mimicking Pituitary Adenoma: A Novel Neuroradiologic Finding. World Neurosurg. 2022;160:1-3. doi: 10.1016/j.wneu.2021.11.075.
34. Boulagnon-Rombi C, Fleury C, Fichel C, Lefour S, Marchal Bressenot A, Gauchotte G. Immunohistochemical Approach to the Differential Diagnosis of Meningiomas and Their Mimics. J Neuropathol Exp Neurol. 2017; 76:289-298. doi: 10.1093/jnen/nlx008.
35. Dridi M, Boutonnat J, Dumollard JM, Peoc'h M, Karpathiou G. Patterns of brachyury expression in chordomas. Ann Diagn Pathol. 2021;53:151760. doi: 10.1016/j.anndiagpath.2021.151760.
36. Doknić M, Pekić S, Miljić D, Soldatović I, Popović V, Stojanović M, Petakov M. Etiology of Hypopituitarism in Adult Patients: The Experience of a Single Center Database in the Serbian Population. Int J Endocrinol. 2017:6969286. doi: 10.1155/2017/6969286.
37. Fukuhara N, Iwata T, Inoshita N, Yoshimoto K, Kitagawa M, Fukuhara H et al. Immunohistochemistry or Molecular Analysis: Which Method Is Better for Subtyping Craniopharyngioma? Endocr Pathol. 2021;32:262-268. doi: 10.1007/s12022-020-09644-z.

38. Poyuran R, Kalaparti VSVG, Thomas B, Kesavapisharady K, Narasimhaiah D. Nonneoplastic and noninfective cysts of the central nervous system: A histopathological study. Neuropathology. 2022. doi: 10.1111/neup.12867. Epub ahead of print.

39. Han SJ, Rolston JD, Jahangiri A, Aghi MK. Rathke's cleft cysts: review of natural history and surgical outcomes. J Neurooncol. 2014;117:197-203. doi: 10.1007/s11060-013-1272-6.

40. Zada G. Rathke cleft cysts: a review of clinical and surgical management. Neurosurg Focus. 2011;31:E1. doi: 10.3171/2011.5.FOCUS1183.

41. Stojanovic M, Manojlovic-Gacic E, Pekic S, Milojevic T, Miljic D, Doknic M, Nikolic Djurovic M, Jemuovic Z, Petakov M. From diabetes insipidus to sellar xanthogranuloma - a "yellow brick road" demanding team-work. Acta Endocrinol (Buchar). 2019;15:247-253. doi: 10.4183/aeb.2019.247.

42. Kim JH, Paulus W, Heim S. BRAF V600E mutation is a useful marker for differentiating Rathke's cleft cyst with squamous metaplasia from papillary craniopharyngioma. J Neurooncol. 2015;123:189-91. doi: 10.1007/s11060-015-1757-6.

43. Doknic M, Savic D, Manojlovic-Gacic E, Savo R, Bokun J, Milenkovic T et al. Clinical case seminar: Familial intracranial germinoma. Endokrynol Pol. 2018; 69:612-618. doi: 10.5603/EP.2018.0060.

44. Al-Aridi R, El Sibai K, Fu P, Khan M, Selman WR, Arafah BM. Clinical and biochemical characteristic features of metastatic cancer to the sella turcica: an analytical review. Pituitary. 2014; 17(6):575-87. doi: 10.1007/s11102-013-0542-9.

45. Baiano C, Somma T, Franca RA, Di Costanzo M, Scala MR, Cretella P et al. Evolution in endoscopic endonasal approach for the management of hypothalamic-pituitary region metastasis: A single-institution experience. Front Oncol. 2022;12:975738. doi: 10.3389/fonc.2022.975738.

46. Pekic S, Stojanovic M, Manojlovic Gacic E, Antic D, Milojevic T, Milicevic M et al. The sellar region as presenting theater for hematologic malignancies-A 17-year single-center experience. Endocr J. 2022; 69:1079-1090. doi: 10.1507/endocrj.EJ21-0790.

47. Pekic S, Bogosavljevic V, Peker S, Doknic M, Miljic D, Stojanovic M t al. Lymphocytic Hypophysitis Successfully Treated with Stereotactic Radiosurgery: Case Report and Review of the Literature. J Neurol Surg A Cent Eur Neurosurg. 2018;79:77-85. doi: 10.1055/s-0037-1604079.

PATOLOGIJA TUMORA SELARNE REGIJE: SAVREMENI DIJAGNOSTIČKI PRISTUP

Emilija Manojlović Gačić[1], Martina Bosić[1], Ivan Zaletel[2], Marko Stojanović[3,4], Mirjana Doknić[3,4], Sandra Pekić Đurđević[3,4], Dragana Miljić[3,4], Dejan Rašić[4,5], Sofija Glumac[1]

Sažetak

Selarna regija je kompleksno područje koje se nalazi u sredini baze lobanje, sa hipofizom u centralnom položaju i bliskim anatomskim odnosom sa vitalnim strukturama, što čini osnovu za razvoj brojnih endokrinoloških i neuroloških stanja uzrokovanih ekspanzijom ili sekretornom aktivnošću tumora. U ovom članku ćemo obuhvatiti literaturu koja sagledava histopatološke i imunohistohemijske aspekte selarnih tumora, zajedno sa kliničkim (pretežno endokrinološkim) karakteristikama, koje su ključni elementi za postavljanje dijagnoze. Predstavićemo histopatološki dijagnostički algoritam za najčešće tumore ovog regiona, neuroendokrine tumore hipofize, kao i tumore zadnje hipofize, meningiome, kraniofaringiome, hordome, tumore germinativnih ćelija, hematološke malignitete, metastaze i ciste Ratkeovog špaga. Savremeni histopatološki dijagnostički pristup selarnim tumorima u velikoj meri zavisi od rutinske upotrebe imunohistohemije za širok spektar antitela, kao i od detaljne korelacije sa endokrinološkim, neurološkim, neurohirurškim i neuroradiološkim aspektima, koji redukuju diferencijalno-dijagnostiče dileme, čime se omogućava izbor najboljih opcija za dalje lečenje pacijenata sa selarnim tumorima.

Ključne reči: selarni tumor, neuroendokrini tumor hipofize, imunohistohemija

Primljen: 12.12.2022. I **Revizija:** 22.01.2023. I **Objavljen:** 25.02. 2023

Medicinska istaživanja 2023; 56(1):67-77