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MINI-REVIEW ARTICLE

NEUROENDOCRINE TUMORS OF THE PITUITARY GLAND – MODERN DIAGNOSTIC APPROACH

NEUROENDOKRINI TUMORI HIPOFIZE – SAVREMENI DIJAGNOSTIČKI PRISTUP

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Abstract

Pituitary neuroendocrine tumors (PitNET) are neuroendocrine tumors originating from adenohypophyseal cells. Although benign, PitNETs sometimes exhibit aggressive biological behavior that was the inspiration for the change of old and traditional name “pituitary adenomas”. Current standard in PitNET diagnostics, according to WHO criteria, is immunohistochemistry, with application of antibodies to adenohypophysis hormones and transcription factors TPIT (T-box family member TBX19), PIT1 (pituitary transcription factor 1) and SF-1 (steroidogenic factor-1) according to which, the line of differentiation is assessed.

In the PIT1 line of differentiation there are somatotroph, lactotroph and thyrotroph tumors. Somatotroph tumors are from PIT1 lineage that produce growth hormone (GH). The WHO defines the following subtypes of somatotroph tumors: densely granulated and sparsely granulated somatotroph tumor.

Lactotroph tumors are the most common neuroendocrine tumors of the pituitary gland. The transcription factors PIT1 and the estrogen receptor α (ERα) play a key role in their genesis. There are two subtypes of lactotroph tumors, densely and sparsely granulated that are differentiated by the type of prolactine (PRL) staining pattern.

Thyrotroph tumors expess both PIT1 and GATA binding protein 3 (GATA3), and can show variable positivity for thyroid-stimulating hormone (TSH).

Beside these three main tumor types of PIT1 lineage, there are mixed lactotroph and somatotroph tumors, mamosomatotroph tumor, acifophilic “stem cell” tumor, mature and immature plurihormonal tumor.

Corticotroph tumors express transcription factor TPIT, and produce adrenocorticotrophic hormone (ACTH). They can be densely granulated and sparsely granulated. Rare subtype of corticotroph tumors, that can show aggressive biological behavior, is Crooke cell tumor.

Gonadotroph tumors are of SF1 lineage of differentiation, and they produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

Null-cell tumors show no distinct cell lineage, and do not express any of the transcription factors. With the use of transcription factors, these tumors are diagnosed through elimination, and their number tented to decrease.

Keywords:
PitNET,
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TPIT,
PIT1,
SF-1

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Sažetak

Neuroendokrini tumori hipofize (PitNET) su neuroendokrini tumori koji vode poreklo od ćelija adenohipofize. Iako benigni, PitNET ponekad pokazuju agresivno biološko ponašanje koje je bilo inspiracija za promenu tradicionalnog imena "adenomi hipofize".
Prema kriterijumima SZO, trenutni standard u dijagnostici PitNET-a je imunohistohemijska analiza, uz primenu antitela prema hormonima adenohipofize i transkripcionih faktora TPIT (*T-box family member TBX19*), PIT1 (*situitary transcription factor 1*) i SF-1 (*steroidogenic factor-1*), prema kojima se određuje linija diferencijacije.
U PIT1 liniji diferencijacije nalaze se somatotrofni, laktotrofni i tireotrofni tumori. Somatotrofni tumori su PIT1 linije diferencijacije i proizvode hormone rasta (GH). Svetska zdravstvena organizacija definiše sledeće potkategorije somatotrofnih tumora: gusto granulirani somatotrofni tumor i oskudno granulirani somatotrofni tumor.
Laktotrofni tumori su najčešći neuroendokrini tumori hipofize. Transkripcioni faktori PIT1 i estrogen receptor α (ERα) imaju ključnu ulogu u njihovoj genezi. Postoje dva podtipa laktotrofnih tumora koji se razlikuju po obrascu bojenja prolaktina (PRL) i to su gusto i oskudno granulirani laktotrofni tumori.
Tireotrofni tumori eksprimiraju PIT1 i GATA, vezujući protein 3 (GATA3), a mogu da pokažu varijabilnu pozitivnost na tireostimulišući hormon (TSH).
Pored ova tri glavna tipa tumora PIT1 linije diferencijacije, u ovoj grupi se nalaze i mešoviti laktotrofni i somatotrofni tumor, mamosomatotrofni tumor, acidofilni tumor "matičnih ćelija", zreli i nezreli plurihormonski tumor PIT1 linije diferencijacije.
Kortikotrofni tumori eksprimiraju transkripcioni faktor TPIT i produkuju adrenokortikotrofni hormon (ACTH). Oni mogu biti gusto i oskudno granulirani. Retki podtip kortikotrofnih tumora, koji može da pokazuje agresivno ponašanje, je Krukov (*Crooke*) ćelijski tumor.
Gonadotrofni tumori su SF1 linije diferencije i oni produkuju folikulostimulišući hormon (FSH) i luteinizirajući hormon (LH).
"Null-cell" tumori ne pokazuju određenu liniju diferencijacije i ne eksprimiraju ni jedan od transkripcionih faktora. Primenom transkripcionih faktora ovi tumori se dijagnostikuju metodom eliminacije, te se njihov broj smanjuje.

Ključne reči:
PitNET,
transkripcioni faktori,
TPIT,
PIT1,
SF-1

Pituitary neuroendocrine tumors (PitNET) are neuroendocrine tumors originating from adenohypophyseal cells (1). They are the most common primary tumors of the selar region and represent 10-15% of all intracranial neoplasms (2). Although benign, PitNETs sometimes exhibit aggressive biological behavior invading surrounding structures, the most commonly cavernous sinuses (3). Unpredictive aggressive biological behavior of PitNET's was the inspiration for a recent proposal of the change of their old and traditional name "pituitary adenomas" (4), which was accepted by the WHO in its latest, fifth classification of endocrine and neuroendocrine tumors (5).

The basic morphological characteristic of PitNET is the destruction of the acinar structure of the adenohypophysis, which can be visualized by histochemical staining on reticulin. It represents a very heterogeneous category from a morphological point of view. There are variations in the size and appearance of cells, cell borders, as well as in the pattern of tumor cell growth (6). The oldest morphological classification of pituitary adenomas (nowadays PitNETs) was based on the tinctorial properties of their cytoplasm assessed on standard hematoxylin-eosin (HE) staining; tumors were classified as acidophilic, basophilic and chromophobic.

Contemporary standard in PitNET diagnostics according to WHO criteria is immunohistochemistry, with mandatory application of antibodies to adenohypophysis hormones and transcription factors TPIT (T-box family member TBX19), PIT1 (pituitary transcription factor 1) and SF-1 (steroidogenic factor-1) (1, 5). They are classified according to the line of differentiation, which is defined by the activation of one of the three transcription factors. The final diagnosis is established in correlation with the expression of the adenohypophiseal hormones, additional transcription factors and clinical data (functional status of the tumor, invasiveness of the tumor, type and duration of symptoms).

A mandatory part of PitNET diagnostics is the assessment of the proliferative Ki-67 index (clone MIB-1) in the area of the highest activity (1, 7). Assessment of immunohistochemical positivity for p53 protein is no longer mandatory according to WHO criteria; it may be useful to predict the aggressive biological behavior of pituitary tumors (1, 5).

Although PitNETs are of epithelial origin, the immunohistochemical expression of cytokeratin (CK) and neuroendocrine markers is not uniform. All PitNETs are positive for Synaptophysin, while the expression of Chromogranin A and CK depends on the type of tumor (2). Persistent CK positivity is observed in somatotroph and corticotroph tumors; other types of PitNETs show variable CK positivity (1, 5).

In addition to the PitNET classification adopted by the WHO, clinical-pathological classification of pituitary tumors has also been proposed. This approach of the classification promotes the use of clinical data, such as tumor size and invasiveness, as diagnostic criteria, in addition to pathohistological and immunohistochemical findings (7,8).

PIT1-lineage PitNETs

Somatotroph tumors

Somatotroph tumors are neuroendocrine pituitary tumors from the PIT1 lineage that produce growth hormone (GH). Excessive, uncontrolled GH secretion clinically leads to acromegaly or gigantism, depending on the age of the patient (1). Clinically silent somatotroph tumors are very rare (9). The WHO defines the following subtypes of somatotroph tumors:

The subtype of densely granulated somatotroph tumor is characterized by diffuse growth pattern and moderate cellularity. They are made up of cells of medium size, with unclear borders. The histological characteristic of this subtype of somatotroph tumor is extremely acidophilic granular cytoplasm. The nuclei are centrally placed, round, slightly uneven, with clear chromatin and conspicuous nucleolus. Immunohistochemically, densely granulated somatotroph tumor cells show diffuse intense staining for low molecular weight cytokeratin (**figure 1A**), which is observed either throughout the cytoplasm or in the perinuclear zone in more than 70% of tumor cells. All tumor cells show diffuse, intense, and uniform immunopositivity for GH (**figure 1B**) and PIT1 (**figure 1C**) (10). Densely granulated somatotroph tumors can be plurihormonal, showing prolactin (PRL) and thyroid stimulating hormone (TSH) staining in addition to GH positivity (1,5).

The subtype of sparsely granulated somatotroph tumor is composed of cells that are medium in size, with unclear borders and chromophobic cytoplasm. The nuclei are mostly round and uneven, with light chromatin and a pronounced nucleolus. Nuclear pleomorphism can be extremely pronounced in this subtype of somatotroph tumor. Double and multinucleate cells are relatively common (10). The diagnostic hallmark of sparsely granulated somatotroph tumors is a round, glassy, light pink round inclusion in the cytoplasm, called the fibrous body, which dislocates the nucleus. On immunohistochemistry, fibrous body is stained with low-molecular cytokeratin (**figure 1D**). Fibrous bodies present in more than 70% of tumor cells represent a diagnostic criterion for differentiating the sparsely granulated somatotroph from the densely granulated tumor subtype (1). Immunohistochemical expression of GH in sparsely granulated somatotroph tumors is typically focal, of low intensity, and sometimes completely absent (**figure 1E**) (10) in contrast to PIT1 positivity, which is diffuse and intensive (**figure 1F**). According to WHO criteria, sparsely granulated somatotroph tumors are classified as high-risk tumors due to their potential aggressive biological behavior (1,5).

All somatotroph PitNETs are characterized by the presence of somatostatin receptors in the cell membrane, especially receptors 2A and 5, which enables their successful therapy with somatostatin analogues (11).

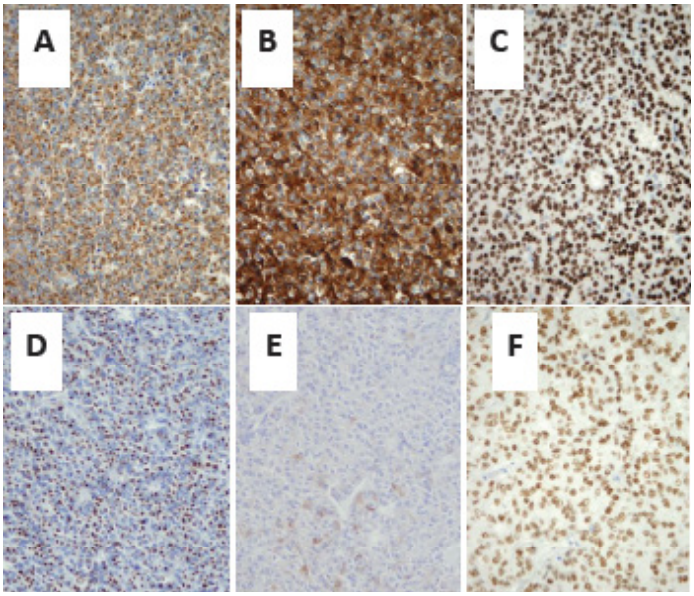

Figure 1. Densely granulated somatotroph PitNETsare characterised by diffuse and intensive cytoplasmic positivity for CK8/18 **(A)** and GH **(B)**, as well as diffuse nuclear positivity for transcriptional factor PIT1 **(C)**. Sparsely granulated somatotroph PitNETs show perinuclear, dot-like, positivity for CK8/18 **(A)** and only focal GH posititity **(B)** which is sometimes absent (x400). Diffuse nuclear positivity for PIT1 confirms PRL/GH/TSH lineage of differentiation **(F)**.

Mixed lactotroph and somatotroph tumors

Mixed lactotroph and somatotroph tumors are composed of two types of tumor cells, which show immunohistochemical positivity for GH or PRL. Their positivity is observed in different cells and in variable ratios. Both granulation patterns can be found in this subtype of somatotroph tumor. Nuclear estrogen receptor α (ERα) positivity is observed in PRL-positive cells (1,5).

Mamosomatotroph tumor

Mamosomatotroph tumor is a rare subtype of somatotroph tumors. Histologically, the tumor is composed of cells in a diffuse growth pattern, with rich acidophilic cytoplasm, large, round, centrally placed nuclei, pale chromatin and accentuated nucleolus. The diagnostic criterion for mamosomatotroph tumor is the immunopositivity of all cells to PRL, GH and ERα (5,12).

Acidophilic "stem cell" tumor

Acidophilic "stem cell" tumors represent up to 1% of somatotroph tumors. They are characterized by diffuse growth pattern of chromophobic and, to a lesser extent, acidophilic cells. Nuclear pleomorphism may be

pronounced. The characteristic morphological features of acidophilic "stem cell" adenoma are vacuoles that represent megamitochondria. Fibrous bodies are observed in the cytoplasm; they can be easy visualized by immunohistochemical staining with low-molecular cytokeratin. Immunohistochemically, acidophilic stem cell tumors show diffuse and intense PRL and ERα immunopositivity, while GH positivity is mild or completely negative (5, 10, 12). Acidophilic stem cell tumors often exhibit aggressive biological behavior (1).

Lactotroph tumors

Lactotroph tumors are prolactin-producing neuroendocrine tumors of the pituitary gland. The transcription factors PIT1 and the ERα play a key role in their genesis (1, 12, 13). The WHO classification of pituitary neuroendocrine tumors recognizes two subtypes of lactotroph tumors, densely and sparsely granulated. The diagnostic criterion for the differentiation of these two types is the PRL staining pattern.

The subtype of sparsely granulated lactotroph tumor is the most common in practice. It is composed of relatively large, sometimes elongated chromophobic cells with unclear cell borders in diffuse or, less frequently, papillary arrangement (**figure 2A**). Psammoma bodies, pronounced congestion and amyloid deposits in the interstitium can be found in this type of tumor. Nuclear and cellular pleomorphism is observed in rare individual cases. Immunohistochemical intensive expression of PRL in the Golgi zone is a morphological hallmark of sparsely granulated lactotroph tumor (**figure 2B**) (1,5). As all lactotroph tumors, immunohistochemical positivity for transcription factor PIT1 is diffuse and intensive (**figure 2C**).

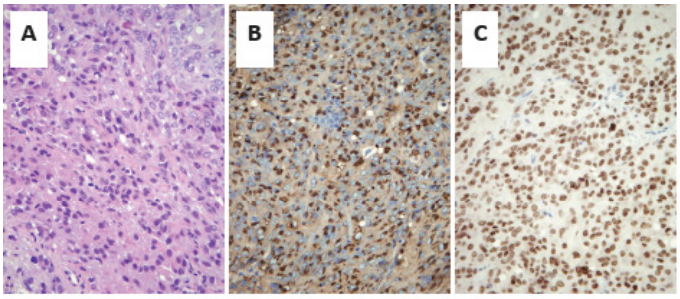

Figure 2. Cells of sparsely granulated lactotroph PitNETs are uniform, with indistinct borders and chromophobic cytoplasm **(A)**. Perinuclear Golgi-type immunohistochemical positivity is typical for sparsely granulated lactotroph PitNETs **(B)**. Nuclear PIT1 positivity denotes PRL/GH/TSH lineage of diffefentiation ***(C)*** (x400).

The densely granulated lactotroph tumor subtype is a very rare tumor subtype, characterized by acidophilic cells with diffuse cytoplasmic PRL immunopositivity (1). This type of tumor may exhibit aggressive biological behavior (14).

Although lactotroph tumors are the most common neuroendocrine tumors of the pituitary gland in clinical practice, their number is very small in surgical series due to the successful use of dopamine agonists in their treatment (15). Surgical treatment is an option only for patients with lactotroph tumors resistant to drug treatment. Dopamine agonists cause morphological changes in lactotroph tumors, such as cell shrinkage, increased nucleo-cytoplasmic ratio, nuclear hyperchromasia, perivascular and interstitial fibrosis, and poor PRL immunopositivity (16).

Lactotroph tumors in men have been recognized by the WHO as tumors with potential aggressive biological behavior (1, 5, 13).

Thyrotroph tumors

Thyrotroph tumors are neuroendocrine tumors of the pituitary gland that are characterized by the production of TSH. Together with somatotroph and lactotroph tumors, they belong to the PIT1 line of differentiation (17). In addition to PIT1, the transcription factor GATA binding protein 3 (GATA-3) is active in thyrotroph tumors (18). Thyrotroph tumors are extremely rare. They are composed of spindle cells with unclear borders, chromophobic cytoplasm, in a solid or diffuse arrangement, with interstitial fibrosis and rare psammoma bodies (1). Immunohistochemically, tumor cells show variable positivity for TSH and the α-subunit (1).

Mature plurihormonal PIT1 lineage tumor

Mature plurihormonal PIT1 lineage tumor is characterized by monomorphic cells positive for the transcription factors PIT1, ER and GATA3. Immunopositivity to GH is dominant; PRL and TSH positivity is focal, and cytokeratin expression is focal and variable (5). These tumors are more often functioning than non-functioning.

Immature plurihormonal PIT1-lineage tumor

Immature plurihormonal PIT1-lineage tumor, previously named "silent subtype 3 tumor", is made up of polygonal or spindle-shaped chromophobe cells that resemble thyrotrophs. The only consistent immunohistochemical staining of these tumors is on the transcription factor PIT1; staining for one or more hormones and transcription factors of PIT1 differentiation lines (GH, PRL, TSH, GATA3, ER and TSH) are variable. Immature plurichormonal PIT1-lineage tumors may be functioning and may cause symptoms of hyperprolactinaemia, acromegaly, or central hyperthyroidism. This type of tumor belongs to the group of tumors with potentially aggressive biological behavior (1, 5).

TPIT-lineage PitNETs

Corticotroph tumors

Corticotroph tumors are neuroendocrine tumors of the pituitary gland that show nuclear expression of the transcription factor TPIT and produce adrenocorticotrophic

hormone (ACTH) (1, 5). The WHO defines three subtypes of corticotroph tumors:

The subtype of densely granulated corticotroph tumor is most frequently observed. It is a functional tumor that causes Cushing's disease. It is composed of monomorphic round cells in diffuse or sinusoidal arrangement with basophilic, PAS positive, cytoplasm (**figure 3A**). The nuclei are mostly round, centrally placed, with a pronounced nucleolus. The diagnostic criterion for densely granulated corticotroph tumor is diffuse and intense immunohistochemical positivity for ACTH (**figure 3B**), low molecular weight cytokeratin and TPIT (**figure 3C**) (1, 19).

The subtype of sparsely granulated corticotroph tumor is less common than densely granulated corticotroph tumor and is most often non-functioning. Tumor cells are larger, and the cytoplasm is chromophobic and mildly PAS positive (**figure 3D**). Immunohistochemically, diffuse and intense cytoplasmic positivity for low molecular weight cytokeratin is observed. Immunopositivity for ACTH is mild and focal (**figure 3E**) (19). In rare cases, immunohistochemical positivity for ACTH is completely absent, when the diagnosis of this type of corticotrophic adenoma depends exclusively on the use of antibodies to the transcription factor TPIT (**figure 3F**) (20). The WHO classifies poorly granulated corticotroph tumors as high-risk group of PitNETs, due to very frequent aggressive biological behavior (1). Aggressive corticotroph tumors often have a mutation in the ATRX gene, which can be detected by immunohistochemical staining (21).

Crooke cell tumor is a rare subtype of corticotroph tumors whose precise histopathological diagnosis is of great importance, since they often show aggressive biological behavior (1). The basic morphological characteristic of the cells of this tumor is Crooke hyaline change in more than 50% of tumor cells. It is characterized by the presence of hyaline, intensely CK-positive material in the form of a ring around the nucleus, which moves ACTH-positive granules into the zone below the cell membrane (22).

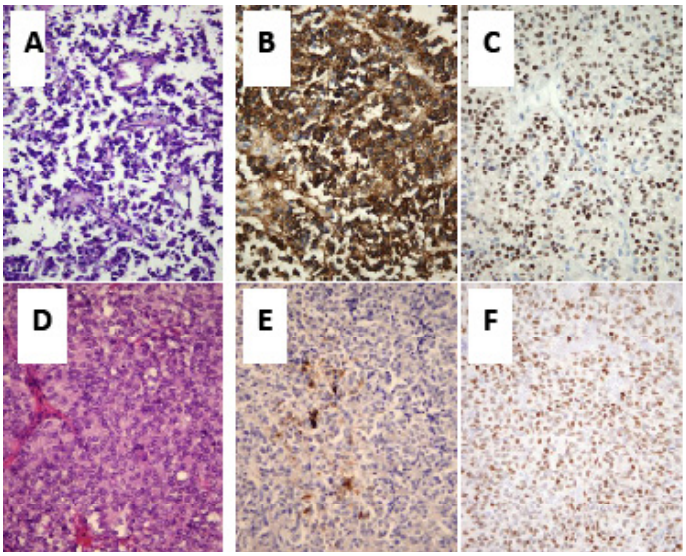

Figure 3. Functional, densely granulated corticotroph PitNETs have basophilic cytoplasm (**A**, HE), diffuse and intensive ACTH immunohistochemical cytoplasmic positivity **(B)** and diffuse intensive nuclear immunohistochemical positivity for transcriptional factor for corticotroph differentiation, TPIT **(C)** Silent corticotroph PitNETs have amphophilic cytoplasm **(D)** and faint ACTH positivity **(E)**. Their diagnosis depends on diffuse TPIT positivity, which denotes its lineage of differentiation **(F)**. (x400).

SF1-lineage PitNETs

Gonadotroph tumors

Gonadotroph tumors are neuroendocrine tumors of the pituitary gland that belong to the SF1 line of differentiation, producing a variable amount of αSU and β subunits of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (23). These tumors are the most common type of non-functioning PitNETs (1).

Gonadotroph tumors are composed of chromophobic cells with clear cell borders that form diffuse sheets or pseudopapillae with conspicuous perivascular pseudorosettes (**figure 4A**). Immunohistochemically, gonadotroph tumors show typical focal expression of αSU, FSH, and LH (**figures 4B and C**), which depends on the visualization technique and may be completely absent (22). The application of immunohistochemical staining to SF1 enabled the recognition of "hormone-negative gonadotroph tumors", which were previously often wrongly classified as "null-cell adenomas" (**figure 4D**) (24). In addition to the transcription factor SF1, gonadotroph tumors also express GATA3 and ERα, the latter being of potential prognostic significance (25).

PitNETs with no distinct cell lineage

Null-cell tumors

Null-cell tumors, also known as "null-cell adenomas", are neuroendocrine tumors of the pituitary gland characterized by the lack of the detection of transcription

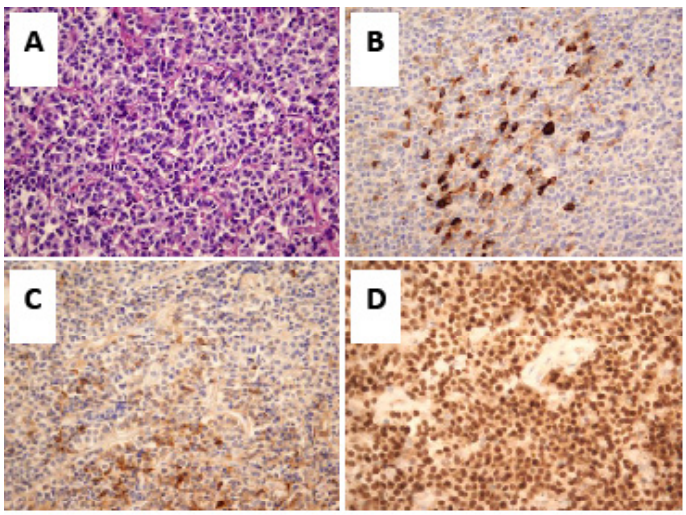

Figure 4. Gonadotroph PitNETs are characterized by perivascular pseudorosettes **(A)**, focal FSH **(B)** and LN **(C)** positivity and diffuse positivity for transcriptional factor for gonadotroph lineage of differentiation - SF1 **(D)** (x400).

factors of the adenohypophysis using immunohistochemistry (1, 5). They are composed of round or polygonal cells with clear cell borders, chromophobic cytoplasm and round, uniform nuclei (1). Owing to the introduction of transcription factors in the diagnosis of pituitary tumors, null-cell tumors have become diagnosed through elimination and their number in surgical series has a significant tendency to decrease (25, 26). Sequencing of PitNET with negative immunohistochemical staining for pituitary transcription factors and hormones, classified them in SF1 of TPIT lineage (27, 28). The negative immunohistochemical staining for transcription factors in these PitNETs could be explained by the low concentration of transcription factors that immunohistochemistry, as a method, was unable recognize; on the other hand, sequencing, as a modern and sensitive method, can detect such low concentrations of transcription factors (27, 28).

Plurichormonal and double tumors

According to the WHO definition, plurichormonal tumors are tumors that produce more than one hormone. This group includes tumors with unusual immunohistochemical combinations of hormone production that cannot be explained by cytodifferentiation (1, 5).

Double tumors consist of two pituitary adenomas of different lineages of differentiation (1, 5). Somatotroph adenomas are most commonly found in double adenomas in surgical series (29).

Conclusion

The group of PitNETs tumors is constantly being reclassified with help of newly developed immunohystochemical stains and molecular techniques. This enables more precise diagnosis and classification of different tumor subtypes. Diagnostic improvement will lead to personalized patients therapy and better prognosis of the disease.

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