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Spindle cell oncocytoma of the adenohypophysis – a clinicopathological and ultrastructural study of two cases

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Abstract

Spindle cell oncocytoma (SCO) of the pituitary gland is a relatively recently established, very rare subtype of adenohypophysis tumours that was introduced as a distinct clinicopathological entity in the fourth edition of WHO classification of the central nervous system tumours (2007). It is non-endocrine neoplasm of the anterior pituitary that occurs in adults and usually follows a benign clinical course, corresponding to WHO grade I. Up to now, pituitary SCO have been reported occasionally and only 14 cases of SCO have been documented in the literature. Because of their rarity, the pathogenesis and natural history of these tumours have not been fully characterized.

We report two additional cases of SCO occurring in females aged 63 years (Case 1) and 65 years (Case 2), who presented with pan-hypopituitarism, headache and visual field defect. In both cases, the magnetic resonance imaging showed solid sellar mass of moderate size with suprasellar extension. The clinical and radiological features suggested non-functioning pituitary macroadenomas without evidence of invasive growth. One patient presented with tumour recurrence 3 years after undergoing the previous surgical removal of tumour, which was initially misdiagnosed as schwannoma. The first tumour was removed by transsphenoidal surgery and the second one by frontal craniotomy.

Histologically and immunohistochemically, both tumours displayed the features typical for SCO of the pituitary. They were composed of interwoven fascicles of spindle cells exhibiting abundant eosinophilic cytoplasm of oncocytic or granular appearance. Mitoses were rarely observed and necrosis was absent. In one case, the advanced lymphocytic infliltration was observed within neoplastic tissue. The tumour cells exhibited immunoreactivity for S-100 protein, galectin-3, vimentin and epithelial membrane antigen but they were negative for GFAP, anterior pituitary neuroendocrine markers (prolactin, growth hormone, TSH, ACTH, FSH, LH), chromogranin, synaptophysin, cytokeratin CK (AE1/AE3), smooth muscle actin, desmin, CD34 and CD68. MIB1 labeling index did not exceed 10%. Ultrastructurally, the tumour cells were rich in mitochondria with lamellar cristae. Moreover, in Case 2 some tumour cells showed a number of giant mitochondria with severely destructed internal matrix.

Spindle cell oncocytoma of the anterior pituitary is often misdiagnosed entity of uncertain histogenesis. It should be considered in the differential diagnosis of various sellar-region lesions of oncocytic morphology.

Key words: pituitary, sellar tumours, spindle cell, oncocytoma.

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Introduction

Spindle cell oncocytoma (SCO) is a rare, benign, non-endocrine neoplasm of the anterior pituitary gland that occurs in adults and follows a benign clinical course corresponding to WHO grade I. This tumour was initially described by Roncaroli *et al.* in 2002 [21] and included as a distinct histopathological subtype of pituitary tumours in the 2007 WHO classification of tumours of the central nervous system [11,18,23].

The clinical and radiological features of SCO are similar to non-functioning pituitary macroadenomas [7,10]. The histological pattern is characterized by non-epithelial spindle cells with abundant eosinophilic, variably oncocytic cytoplasm exhibiting conspicuous accumulation of mitochondria. The neoplastic cells are immunoreactive for EMA, vimentin and galectin-3 but are negative for pituitary hormones [11]. To date, only 14 cases of SCO have been reported in the literature [3,5,6,8,10,17,21,26]. The prognosis of SCO remains uncertain, as long-term follow-up study in most reported cases is not yet available.

We present two additional cases of this unusual entity to evaluate its immunomorphological and ultrastructural profile. These cases of SCO occurred in females aged 63 years (Case 1) and 65 years (Case 2), who presented with pan-hypopituitarism, headache and visual field defect. Clinically and radiologically both tumours suggested non-functioning pituitary macroadenomas. One patient was admitted with tumour recurrence appearing 3 years after first surgery. The primary tumour, initially misdiagnosed as schwannoma, was removed by transsphenoidal surgery and the second one by frontal craniotomy. For purpose of this report, retrospective analysis of the biopsy material from sellar-region lesions originally diagnosed as non-functional and oncocytic tumours during a period of 12 years (from 1998 to 2010) was performed.

Material and methods

The biopsy tumour specimens were fixed in 10% formalin, embedded in paraffin and routinely stained with hematoxylin and eosin (H&E). Immunohistochemical staining was performed on paraffin-embedded specimens according to the labelled EnVision Flex Visualization System (Dako, K8000) with DAB as chromogen using antibodies against: S-100 protein (dilution 1 : 3000), vimentin (dilution 1 : 100), epithelial membrane antigen (EMA, dilution 1 : 100), glial fibrillary acidic protein (GFAP, dilution 1 : 100), smooth muscle actin (SMA, dilution 1 : 100), desmin (dilution 1 : 100), CD34 (dilution 1 : 100), CD68 (dilution 1 : 100), chromogranin A (dilution 1 : 100), synaptophysin (dilution 1 : 100), cytokeratin AE1/AE3 (CK, dilution 1 : 100), Ki-67 (MIB1, dilution 1 : 100) – all antibodies from Dako; galectin-3 (dilution 1 : 100, Novocastra), anterior pituitary hormones or subunits: prolactin (PRL, dilution 1 : 200), growth hormone (GH, dilution 1 : 500), ACTH (dilution 1 : 500), β-TSH (dilution 1 : 200), β-FSH (dilution 1 : 500), β-LH (dilution 1 : 500) – all antibodies from LAB VISION and the glycoprotein α-subunit (dilution 1 : 100, Novocastra). MIB-1 labeling index was established.

For electron microscopy, the small pieces of tissue were fixed in 2.5% cold glutaraldehyde for 1 hour, washed in cacodylate buffer, postfixed in 1% osmium tetroxide, dehydrated in graded alcohols and embedded in Epon 812. Ultrathin sections were counterstained with uranyl acetate and lead citrate and examined in a Philips CM 120 BioTWIN electron microscope.

Results

Case 1

A 63-year-old woman was admitted to Neurosurgical Department with a diagnosis of clinically endocrine inactive anterior pituitary adenoma. She presented with a 3-year history of worsening headache and vertigo with symptoms of fatigue and sleepiness of several months duration. During the last 3 month she suffered from nausea and transitional morning vomiting. She lost her weigh about 10 kg and developed the edema of her face and legs. Examination of her visual fields revealed a bitemporal hemianopsia. Preoperative laboratory endocrine tests showed discrete prolactin (PRL) evaluation, marked decrease of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), very low range of estradiol and progesterone with signs of hipogonadotropic hypogonadism and very low range of cortisol. The thyroid-stimulating hormone (TSH) was within normal range with low fT3 and fT4 secretion.

The magnetic resonance imaging (MRI) demonstrated a solid, well-defined, homogeneously enhancing mass in the pituitary region, measuring 21 × 18 × 19 mm (Fig. 1). The tumour mass expanded the sella turcica and caused deformity and effacement of the optic chiasm. The cavernous sinuses were not

involved. The tumour was gross totally removed by transsphenoidal surgery. The patient was recommenced on replacement therapy with hydrocortisone and Eltroxin. After 7 weeks the dose of Hydrocortison was reduced. No recurrences were noted at the 28-month follow-up examinantion.

Pathological findings

Histopathologically, the tumour was composed predominantely of compact, interwoven fascicles of plump spindled cells with abundant eosinophilic, often oncocytic or finely granular cytoplasm (Fig. 2A). Cell nuclei exhibited mild atypia and hyperchromasia and only focally nuclear polymorphism could be observed (Fig. 2B). Mitoses were seen sporadically and necrosis was absent. The rich numerous lymphocytic infiltration within neoplastic tissue was observed.

Immunohistochemically, the majority of tumour cells were immunoreactive for vimentin (Fig. 3A), S-100 protein (Fig. 3B) and epithelial membrane antigen (Fig. 3C). The neoplastic cells exhibited intense cytoplasmic immunostaining for anti-mitochondrial antibody – galectin-3 (Fig. 3D) but they were immunonegative for GFAP (Fig. 4A), anterior pituitary hormones (Fig. 4B) (prolactin, growth hormone, TSH, ACTH, FSH, LH, glycoprotein α-subunit), chromogranin, synaptophysin, CK (Fig. 4C), smooth muscle actin, desmin, CD34 and CD68. The MIB1 labeling index was about 5% with focal increase of proliferation activity (Fig. 4D).

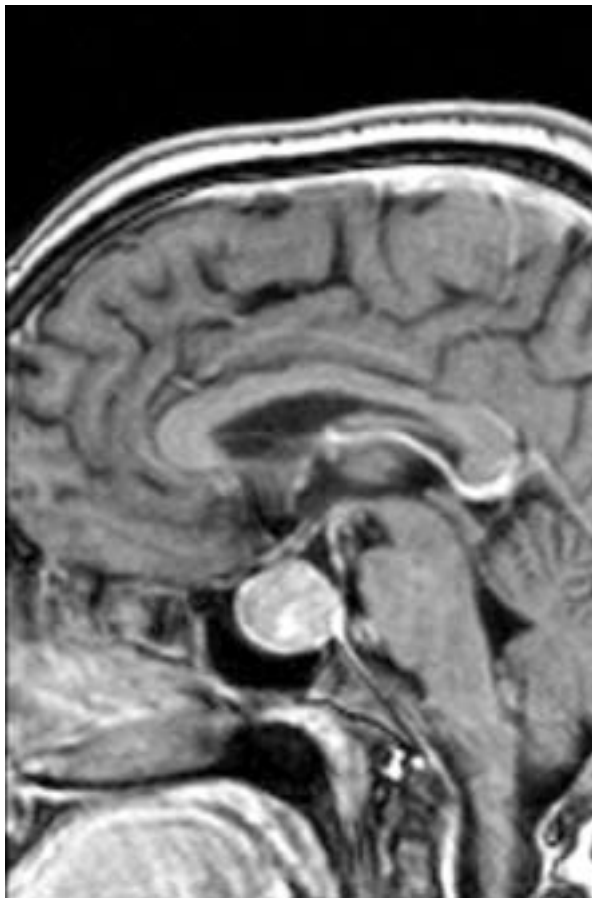

Fig. 1. Sagital MR imaging scan of the brain. A solid, well-demarketed, homogeneously enhancing, noninvasive mass in the pituitary region.

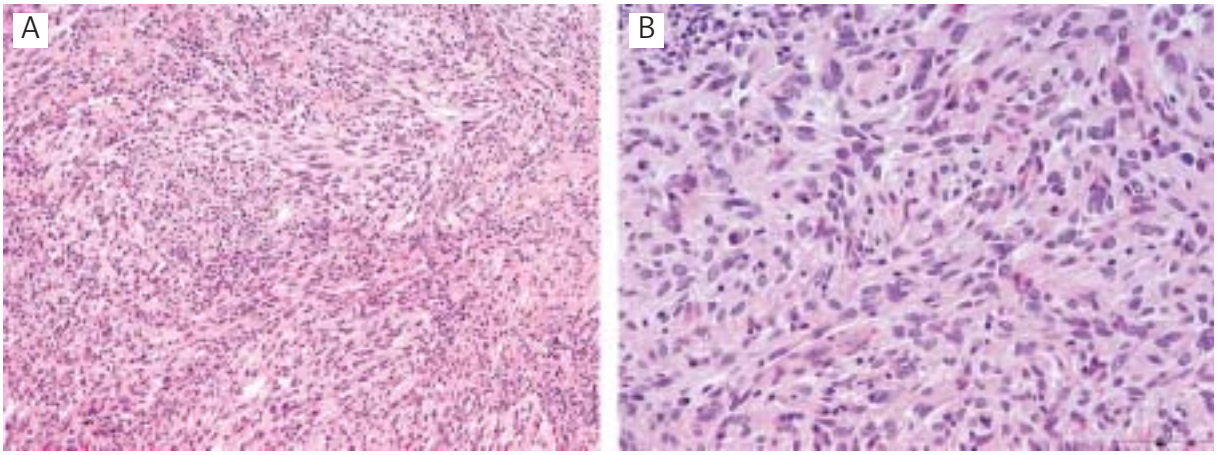

Fig. 2. Case 1. Histopathology of spindle cell oncocytoma. **(A)** Interwoven fascicles of spindled cells, H&E, x 10; **(B)** Spindle or plump cells exhibiting oncocytic or finely granular eosinophilic cytoplasm and moderate nuclear atypia, H&E, × 20.

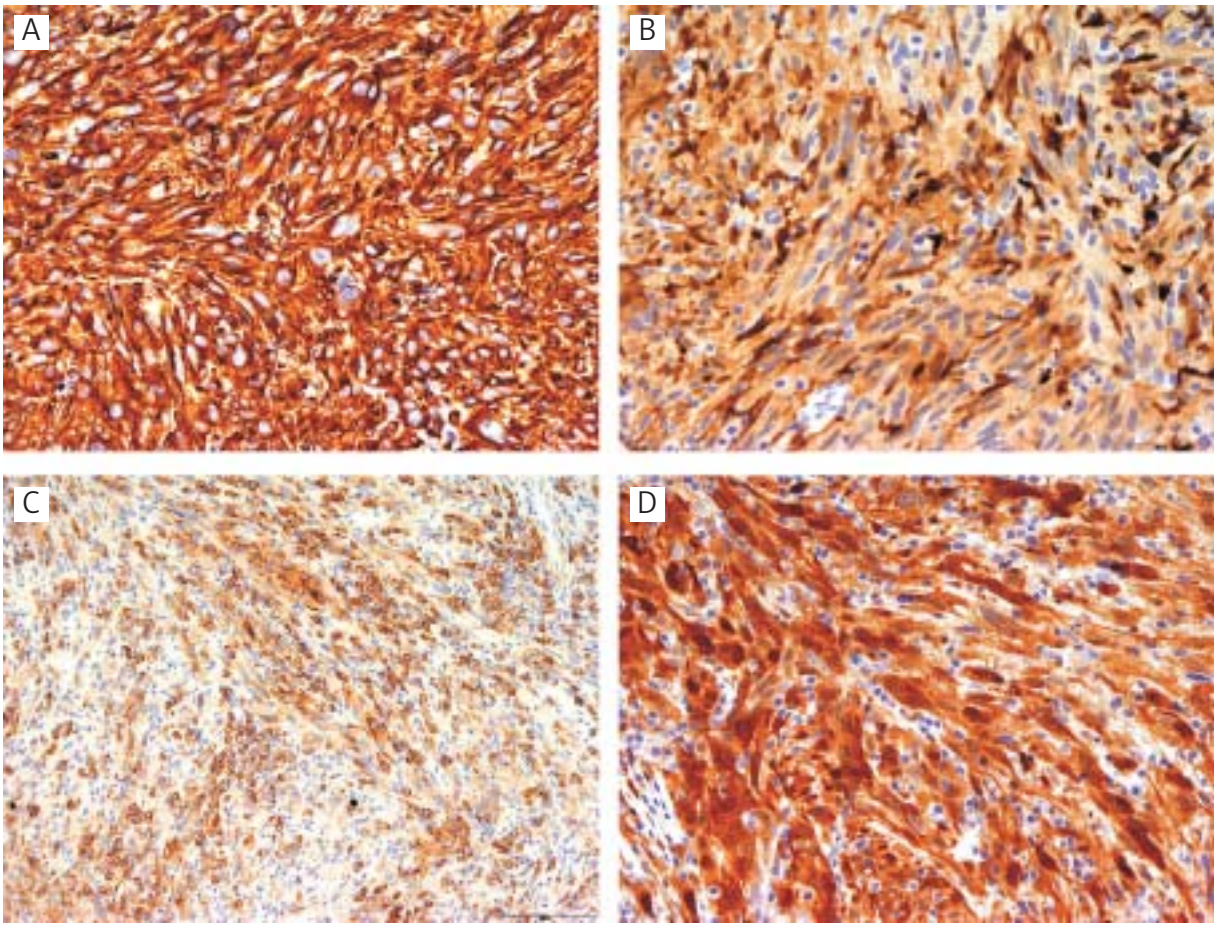

Fig. 3. Case 1. Immunohistochemical features of SCO. **(A)** Neoplastic cells with diffuse immunoreaction for vimentin, × 20; **(B)** Immunopositivity for S-100 protein, × 20; **(C)** Focal reactivity for EMA, × 10; **(D)** Numerous cells strongly immunopositive for Gal-3, × 20.

Ultrastructurally, the neoplastic cells displayed spindle and polygonal morphology. Their cytoplasm revealed accumulation of mitochondria with lamellar cristae (Fig. 5). The intermediate intercellular junctions and well-formed desmosomes could be seen. The lysosomes were present, sometimes surrounded by bundles of intermediate filaments. No secretory granules were identified.

Case 2

A 65-year-old woman was admitted to Neurosurgery Department with symptoms of pituitary tumour recurrence. She was initially operated due to a well defined, sellar-region mass measuring 25 × 13 × 16 mm. At first admission, she presented with pituitary hormone insufficiency and bitemporal hemianopsia. The clinical and preoperative imaging features lead to preoperative diagnosis of a non-functioning macroadenoma. The primary tumour was removed by transsphenoidal surgery, followed by histopathological diagnosis of schwannoma. Three years later, neuroimaging demonstrated recurrence of sellar-region tumour. Preoperative endocrine studies showed pituitary hormone insufficiency, including a low range of cortisol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), growth hormone (GH) and thyroid-stimulating hormone (TSH). On MRI studies the tumour measured 18 × 19 × 21 mm and exhibited a significant suprasellar extension. The tumour was gross totally excised by frontal right craniotomy. Pathological examination of the material from both surgery established the diagnosis of spindle cell oncocytoma in both, primary and recurrent tumour. A pituitary hormonal profile was consistent with pan-

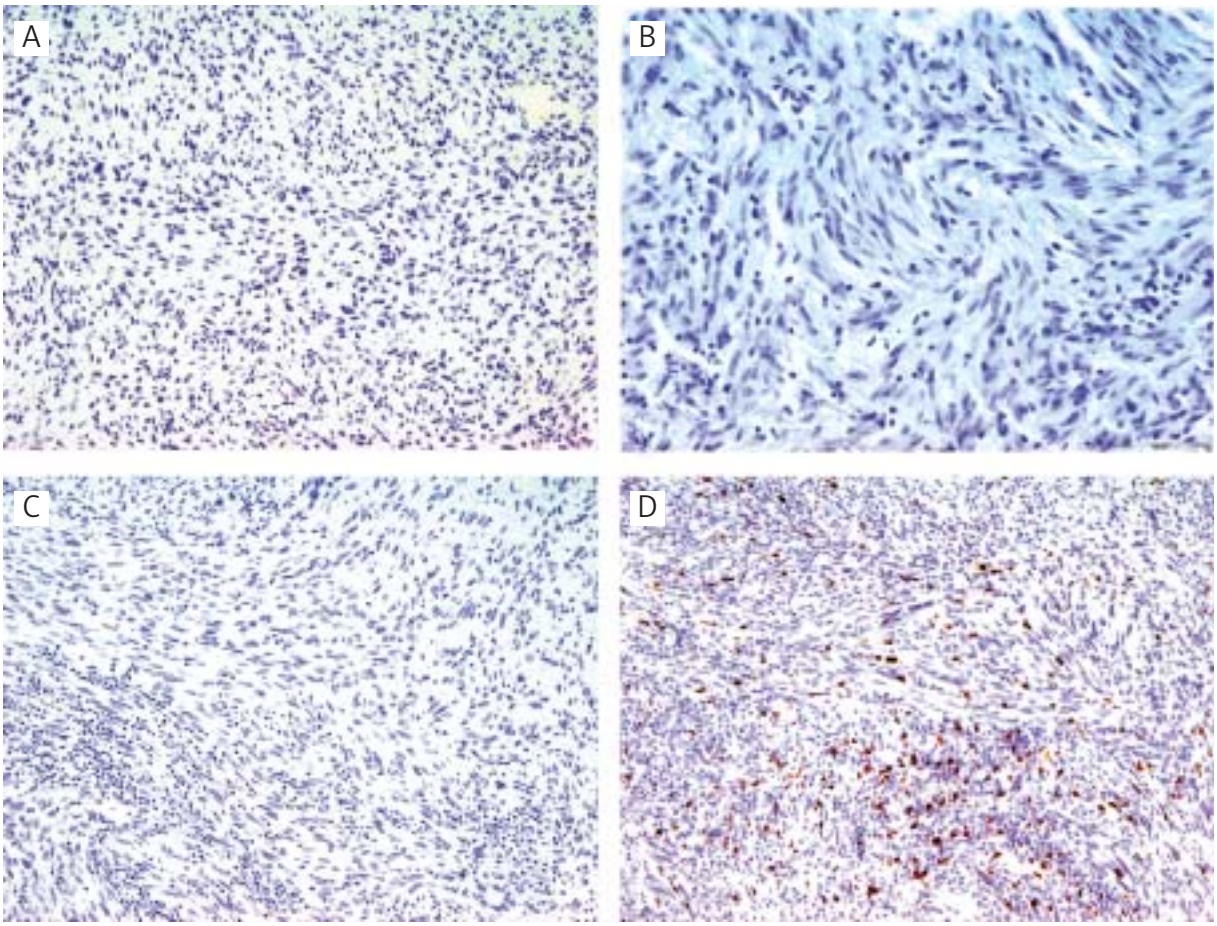

Fig. 4. Case 1. Immunohistochemical features. **(A)** No immunoreactivity for GFAP, × 10; **(B)** No immunoexpression of glycoprotein α-subunit, × 20; **(C)** No expression of cytokeratin AE1/AE3, × 10; **(D)** Ki-67 labeling index, × 10.

hypopituitarism. Twenty months after surgery there was no evidence of tumour recurrence.

Pathological findings

Histopathologically, the neoplastic tissue from the primary and recurrent tumour revealed the identical pattern. Both tumours were composed of spindled or epithelioid cells arranged in interlacing fascicles. Majority of cells exhibited abundant eosinophilic cytoplasm, often with oncocytic or granular features (Fig. 6A). Mitoses were seen only occasionally and necrosis was absent.

Immunohistochemically, the tumour cells were positive for vimentin (Fig. 6B), S100 protein (Fig. 6C) and focally positive for EMA (Fig. 6D). Tumour exhibited strong immunostaining of galactin-3 (Fig. 6E). Tumour cells were immunonegative for pituitary hormones (GH, PRL, FSH, LH, TSH, ACTH), GFAP, CK (AE1/AE3), GFAP, SMA, CD34, CD68 and neuroendocrine markers chromogranin and synaptophysin. The MIB-1 labelling index was about 1% in the original tumour and in the recurrent neoplasm (Fig. 6F).

Ultrastructurally, the majority of cells exhibited elongated cells with irregular surfaces and numerous long, interlacing processes. The cytoplasm of neoplastic cells were packed with abundant mitochondria with lamellar structures (Fig. 7A). Some cells exhibited enlarged, sometimes giant mitochondria with disrupted cristae (Fig. 7B). The intermediate junctions were seen occasionally. A few lysosomes were seen but there were no neurosecretory granules.

Discussion

Pituitary adenomas represent about 90% of all mass lesions of sella turcica and 10-20% of all intracranial tumours. According to 2004 WHO classifi-

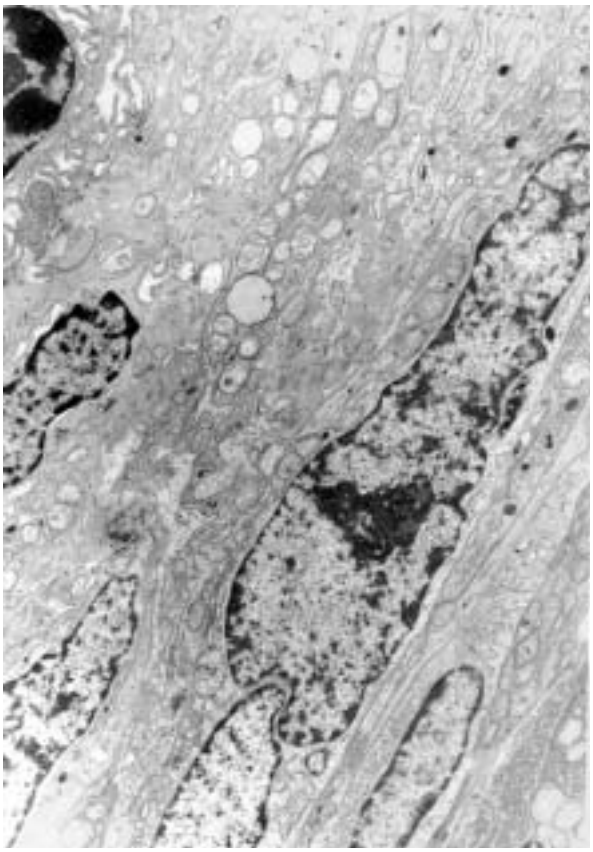

Fig. 5. Ultrastructure of SCO. The neoplastic cells of spindle morphology with accumulation of swollen mitochondria exhibiting disrupted lamellar cristae. Intermediate junctions are seen. Original magn. × 2850.

cation of neuroendocrine tumours [1] and forth edition of 2007 WHO classification of nervous system tumours [11], the mass lesions of pituitary region include pituitary adenomas, pituitary carcinoma, hyperplasia of pituitary gland and other primary neoplasms of sella turcica i.e. craniopharyngioma, Ratke cleft cysts, meningioma, chordoma, gangliocytoma, astrocytoma, granular cell tumour, lymphoma, germinoma, hemangiopericytoma and spindle cell oncocytoma.

Spindle cell oncocytoma (SCO) is a rare, recently identified non-endocrine sellar-region lesion that manifests in adults with clinical presentation indistinguishable from other functionally inactive, non-hormone-producing macroadenomas [6,17]. SCO of the adenohypophysis may arise as an intrasellar, suprasellar, or intrasellar/suprasellar mass, sometimes invading the cavernous sinus. On MR images this tumour is of solid appearance with contrast enhancement, similar to pituitary macroadenomas. To date, pituitary spindle cell oncocytomas have been reported sporadically and only 14 cases of SCO was documented in the literature [3,5,6,8,10,17,21,26]. The reported cases were in adults ranging from 26 to 71 years (mean: 56 years). The majority of them presented with pan-hypopituitarism and visual defects, nausea, vomiting or headache. The incidence of SCOs is difficult to determine, but Kloub *et al*. [17] accounted for approximately 0.4% of all operated sellar tumours. The majority of documented SCOs represent lesions of a benign clinical course, corresponding to WHO grade I and characterized by favorable prognosis. Numerous cases exhibited the long lasting follow-up without recurrences after subtotal resection and proton beam therapy [6]. However, some reports demonstrated recurrences of SCO after the initial tumour resection and documented high Ki-67 labeling, mitotic activity and necrosis, indicating the more aggressive clinical behavior of these lesions [17]. One report evidenced late recurrence with subclinical intratumoral bleeding [2]. Also one of our patients undergone initial surgery with tumour resection followed by tumour recurrence after 3 years.

We performed the retrospective analysis of sellar-region lesions originally diagnosed as nonfunctional and oncocytic tumours. During a period of 12 years (from 1998 to 2010), the re-review of surgical specimens of two thousand unselected tumours of adenohypophysis from Poland established the diagnosis of SCO only in two presented herein cases of pituitary tumours. This data supports the rarity of this entity.

The differential diagnosis of SCO ought to consider different oncocytic and/or granular cell lesions of pituitary region [12,24]. Various sellar mass lesion might be confused with spindle cell oncocytoma of pituitary, including schwannoma, pituitary adenoma with oncocytic change, oncocytic null cell adenoma, granular cell tumour, pituicytoma, paraganglioma, meningioma with oncocytic features and solitary fibrous tumour. These neoplasms of different histogenesis might be more or less spindled in appearance and often associated with oncocytic changes. The detailed immunohistochemical studies are helpful in differential diagnosis. The differentiation of SCO and oncocytic pituitary adenoma is important as the second one is of higher aggressiveness. Most cases of pituitary adenomas reveal immunoreactivity for chromogranin, synaptophysin and/or selected pituitary

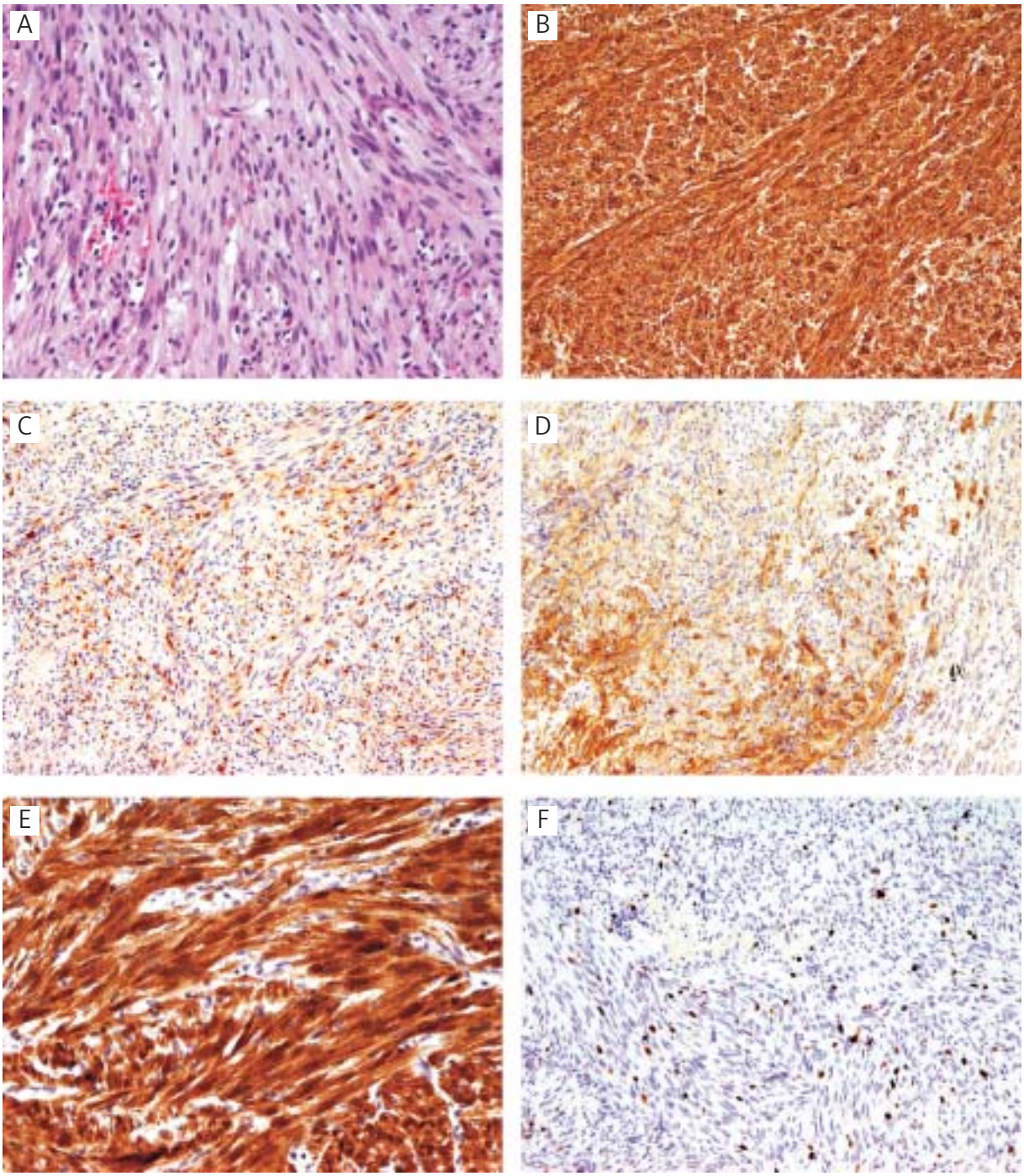

Fig. 6. Case 2. Histopathology and immunohistochemistry of pituitary tumour – material from initial surgery. **(A)** Tumour composed of elongated bipolar, spindle cells with eosinophilic, finely granular cytoplasm, H&E, × 20; **(B)** Neoplastic cells exhibiting diffuse immunoreactivity for vimentin, × 10; **(C)** Slight expression of S-100 protein, × 10; **(D)** Focally immunopositivity for EMA, × 10; **(E)** Strong immunopositivity for Gal-3, x 20; **(F)** Ki-67 labeling index, × 10.

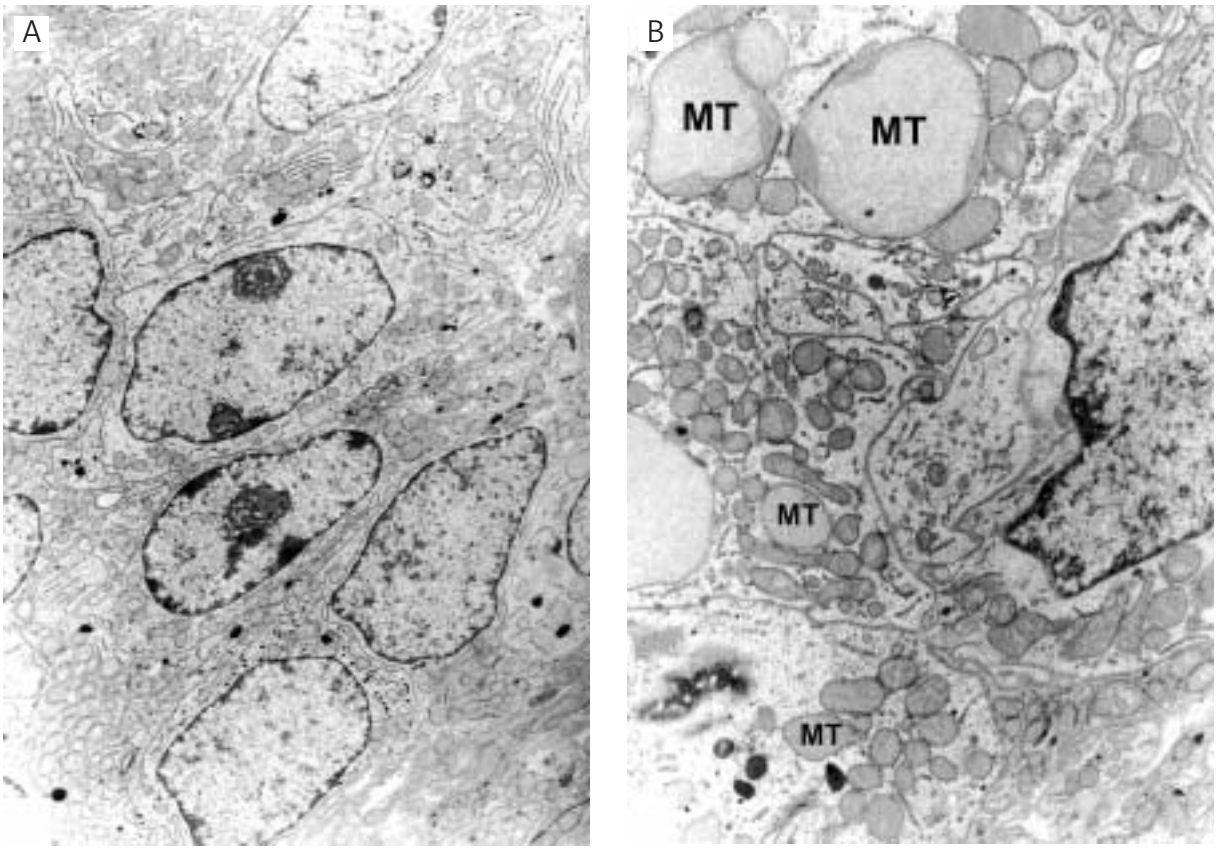

Fig. 7. Ultrastructural features of SCO. **(A)** Oncocytic, spindle or polygonal neoplastic cells with cytoplasm packed with mitochondria. Intercellular junctions with well-formed short desmosomes seen between adjacent cells. Original magn. × 2850; **(B)** Neoplastic cells exhibiting accumulation of pleomorphic and giant cell mitochondria (MT) with completely disrupted cristae. Original magn. × 4800.

hormones. A subtype of null cell adenoma with oncocytic changes have a higher risk of recurrence after radiotherapy, thus their correct diagnosis is of clinical importance. Granular cell tumours of neurohypophysis usually lack the typical spindle cell morphology characteristic for SCO. These tumours are composed of plump or polygonal cells with eosinophylic, granulated and PAS-positive cytoplasm. Moreover, the granular cells are not strongly positive for S-100 protein. The differential diagnosis of pituicytoma was also essential. These tumours are derived from the glial stroma of neurohypophysis and exhibit spindle and epithelioid cell morphology. Pituicytomas are vimentin and S-100 protein positive but usually lack EMA reactivity and show glial fibrillary acidic protein expression [4]. Also oncocytic meningioma, an unusual variant of meningioma with aggressive behavior and recurrences, ought to be taken into consideration in differential diagnosis of sellar-region tumours and immunohistochemical features are important for critical diagnosis [22].

Our two presented cases demonstrated the characteristic clinicopathological features of spindle cell oncocytoma of the adenohypophysis. Our second case was initially considered as intrasellar benign nerve sheath tumour due to its S-100 protein positivity typical for schwannomas and immunonegativity for pituitary hormones. However, the primary tumour lacked the histological pattern of Antoni A or B morphology and the final diagnosis of SCO was established based upon combined morphologic, immunohistochemical and ultrastructural features.

The main ultrastructural characteristics of SCOs include cytoplasmic accumulation of mitochondria, whereas the secretory granules and desmosomes are

rarely encountered [6,17,21]. The neoplastic cells of SCOs exhibited only a few lysosomes in contrast to granular cells observed in granular astrocytomas, which cytoplasm was filled with electron-dense granular material limited by a single membrane and autophagic vacuoles, whereas numerous condensed electron-dense, bizarrely-shaped mitochondria were observed only occasionally [25]. Moreover, in Case 2 some tumour cells showed a few giant mitochondria with severely destructed internal matrix, the feature not previously described in SCOs.

The nature and histogenesis of SCO remains uncertain, nevertheless both immunohistochemical and ultrastructural features of these unique lesion suggest its derivation from folliculostellate cells (FSCs) of the adenohypophysis [9,13,21]. FSCs are heterogeneous, non-hormone secreting stellate cells of the anterior pituitary, that represent about 5-6% of all cells in the adenohypophysis and provide a structural sustentacular elements for the endocrine cells [14,15]. FSCs are considered as a type of stem cells in the adult pituitary gland [14,15]. These cells are immunopositive for S-100 protein, vimentin, EMA and occasionally GFAP [11,14,23,27]. Recent studies have demonstrated expression of galactin-3 in the human pituitary restricted to FSCs and ACTH and PRL producing adenomas [11,16,19-21]. The ultrastructural features of FSCs suggest that FSCs may represent an adult stem cell progenitor population.

Concluding, the diagnosis of SCOs in reported herein two cases of pituitary tumours, one of which was recurrent, was confirmed by immunohistochemical and ultrastructural profiles. Clinically and radiologically these tumours suggested nonfunctioning pituitary macroadenomas. The tumours were less than 25 mm in diameter and they did not reveal invasive growth. The immunorectivity for vimentin, S100, and galectin-3 was consistent with diagnosis of spindle cell oncocytoma and the tumours displayed characteristic ultrastructural features, especially presence of numerous swollen mitochondria with lamellar cristae and short intercellular junctions, without neurosecretory granules.

Both, immunohistochemical and electron microscopic examination is essential for distinguishing SCO from other entities with overlapping oncocytic features. In the current WHO classification, the SCO corresponds to grade I, but its prognosis and biologic spectrum remains uncertain and long-term follow-up is required.

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