S100 protein expression in pituitary adenomas

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Abstract

Background: The predicting of pituitary tumor behavior remains one of the most incurable medical problems. One of the causes is poor correlation between the morphology of pituitary tumors and their clinical aggressiveness.
Material and methods: 96 cases included in our study have been microscopically investigated on specimens colored with eosin haematoxylin by three experienced pathologists according to WHO recommendations. Out of these ten cases were represented by normal pituitary tissue to make it possible to compare the typical pituitary morphology with the microscopic appearance of various types of pituitary adenomas.
Results: In both the normal pituitary gland and in pituitary adenomas, endothelial cells presenting a nuclear expression for S100 were occasionally observed. The percentage of positive cases for protein S100 was 66.12% from the total number of cases. Amongst these, 39.02% presented a compact growth pattern, 39.04% were of papillary type, 9.75% presented a trabecular growth pattern, 4.87% spindle-shaped and 7.31% were of alveolar type. Papillary type pituitary adenomas registered the highest intensity of expression for protein S100 in tumor cells. The acidophilic cells were present in a percentage of 34.2% of cases. Pituitary adenomas with basophilic cells represented a percentage of 26.8% of positive cases for protein S100, and, for 39% of cases the chromofobe component was present forming pure chromofobe pituitary adenomas or mixed chromofobe-acidophilic/basophilic pituitary adenomas.
Conclusions: Protein S100 expressions in tumor cells is implicated in the pathogenesis of the growth hormone and prolactin secreting pituitary adenomas, the mechanisms of activation being nowadays incompletely studied. Through analogy with the observations obtained in other tumor types, it is possible that S100 pituitary adenomas to represent a group of pituitary adenomas with an aggressive behavior and a high capacity of invasion and recurrence, aspects that represent an unfavorable prognostic factor.
Key words: S100 protein, human pituitary adenoma.

Introduction

Predicting of pituitary tumor behavior remains one of the most incurable medical problems. One of the causes is poor correlation between the morphology of pituitary tumors and their clinical aggressiveness. Pituitary tumors have been strongly scrutinized for their immunohistochemical expression of a wide range of proteins, growth factor, cytokines and various gene products in hope to find prognostic markers. The aims of the present work were to study the presence and distribution of S100 protein-immunoreactive cells to assess their response in cases of various types of pituitary adenomas. Protein S100 was originally isolated in the central nervous system and has been localized in folliculo-stellate sells of the anterior lobe of the pituitary gland.

Material and methods

The research was carried out at the Department of Morphopathology of Nicolae Testemitsanu State University of Medicine and Pharmacy in 2012-2015 period. The research protocol has got the Research Ethics Committee approval (protocol No 52 of 08.06.2015)

96 cases included in our study have been microscopically investigated on specimens colored with eosin haematoxylin by three experienced pathologists according to WHO recommendations. Out of these ten cases were represented by normal pituitary tissue to make it possible to compare the typical pituitary morphology with the microscopic appearance of various types of pituitary adenomas.

The studied samples were taken from the postoperative pieces (surgically removed pituitary adenomas), which were set in a 4% formalin solution buffered at pH 7.2 for 48-72 hours and placed into paraffin, using the common histological technique Thermo Shandon standardized and automated system (Thermo Fisher Scientific Inc., Waltham, MA, USA). The microscopy was performed using Nikon Eclipse E600 microscope (Nikon Corporation, Tokyo, Japan), the images being taken with Coolpix 950 digital camera in JPEG format. The data are presented as absolute and relative expressions (%).

Results

Protein S100 in pituitary adenomas was also studied by using the immunohistochemical method on the normal pituitary gland and in pituitary adenomas. Protein S100 proved to have a nuclear and cytoplasmic pattern, being positive in the stellate follicular cells but also in the endocrine cells of the normal pituitary gland (fig. 1) and the adenomatous ones.

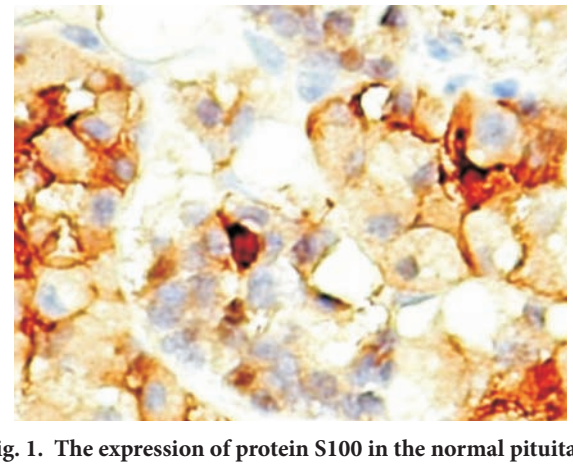

Fig. 1. The expression of protein S100 in the normal pituitary gland. Note the intense, nuclear and cytoplasmic expression in the stelate follicular cells and the moderate cytoplasm-restricted expression in the endocrine cells with an acidophilic pattern on hematoxilin-eosine and a low intensity in chromofobe cells.

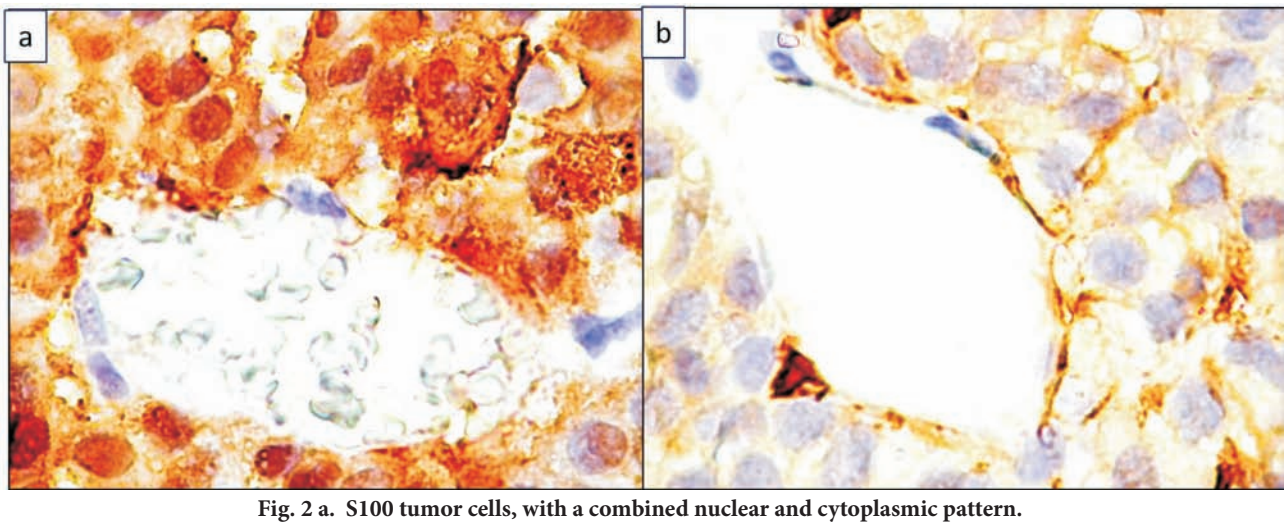

Fig. 2 a. S100 tumor cells, with a combined nuclear and cytoplasmic pattern.
Fig. 2 b. S100 tumor cells, exhibiting a cytoplasmic pattern.

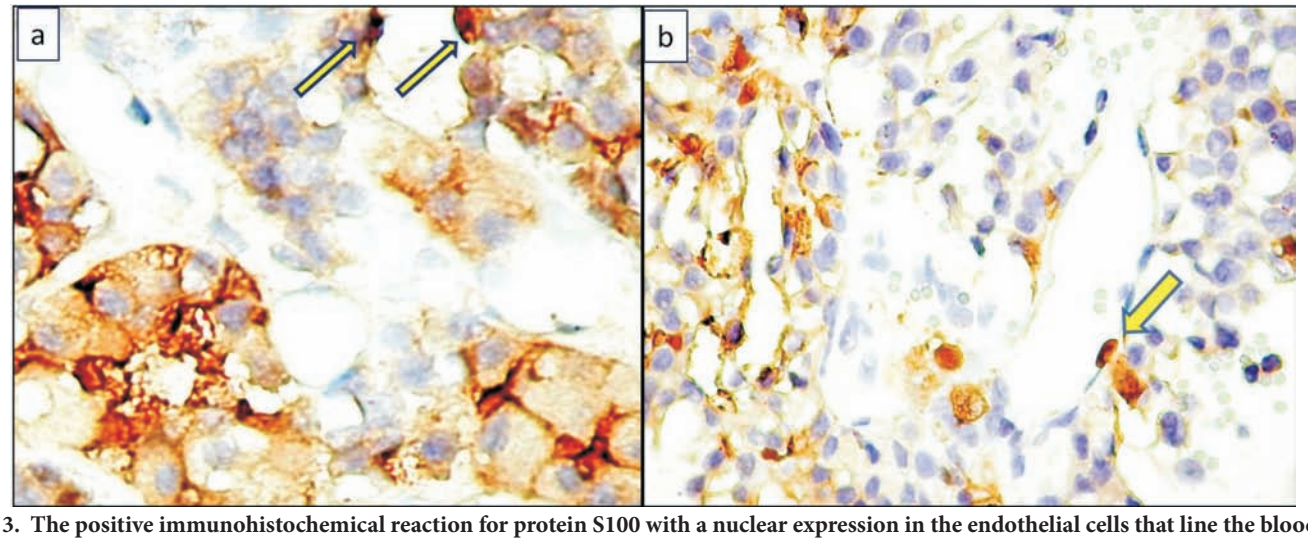

Fig. 3. The positive immunohistochemical reaction for protein S100 with a nuclear expression in the endothelial cells that line the blood capillaries from the normal pituitary gland (a, arrow) and from the vessels belonging to pituitary adenomas (b, arrow).

The combined nuclear/cytoplasmic pattern was observed in tumor cells in only 19.5% of S100 positive cases (fig. 2 a), the rest of the cases presenting a cytoplasm-restricted expression (fig. 2 b).

In both the normal pituitary gland and in pituitary adenomas, endothelial cells presenting a nuclear expression for S100 were occasionally observed (fig. 3 a, b).

The percentage of positive cases for protein S100 was 66.12% from the total number of cases. Amongst these, 39.02% presented a compact growth pattern, 39.04% were of papillary type, 9.75% presented a trabecular growth pattern, 4.87% spindle-shaped and 7.31% were of alveolar type. Papillary type pituitary adenomas registered the highest intensity of expression for protein S100 in tumor cells (fig. 4a). With the exception of papillary type adenomas, in the majority of pituitary adenoma cases the intensity of the reaction was low and moderate, in comparison with the normal tissue (fig. 4b).

The acidophilic cells were present in percentage of 34.2% of cases. Pituitary adenomas with basophilic cells represented percentage of 26.8% of positive cases for protein S100, and, in 39% of cases the chromofobe component was present forming pure chromofobe pituitary adenomas or mixed chromofobe-acidophilic/basophilic pituitary adenomas.

Regarding the particularities of the immunohistochemical expression of protein S100, we observed variabilities in the presence, intensity and distribution of this marker in relation to the hormone profile. Growth hormone secreting pituitary adenomas proved to be extremely hetherogenous in what is considered the expression of protein S100 in tumor cells. The cases ranged from the absence of its expression in tumor cells (stellate follicular cells being positive, fig. 5 a) to a low expression, strictly located in the cytoplasm (fig. 5 b), an intense expression, in the entire tumor area, nuclear and cytoplasmic (c) or just cytoplasmic (d).

In case of pituitary adenomas with chromofobe cells, the expression of protein S100 was low in the cytoplasm of the chromofobe cells, being mostly nuclear restricted (fig. 6).

Tumor cells were negative for protein S100. On the other

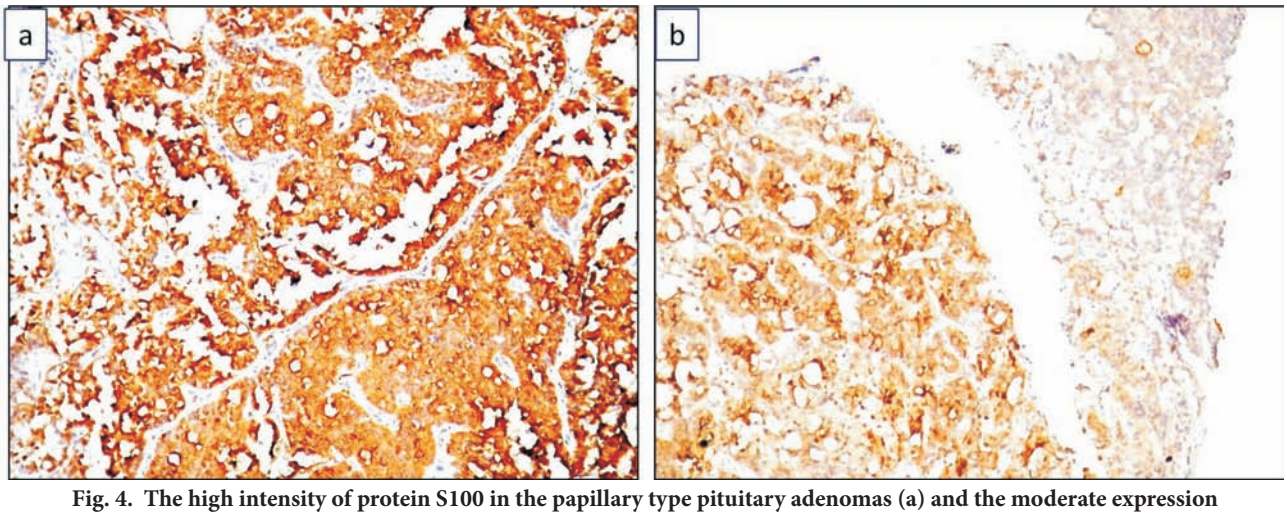

Fig. 4. The high intensity of protein S100 in the papillary type pituitary adenomas (a) and the moderate expression in the adenomatos tissue (b, right section) compared to the normal pituitary gland (b, left section).

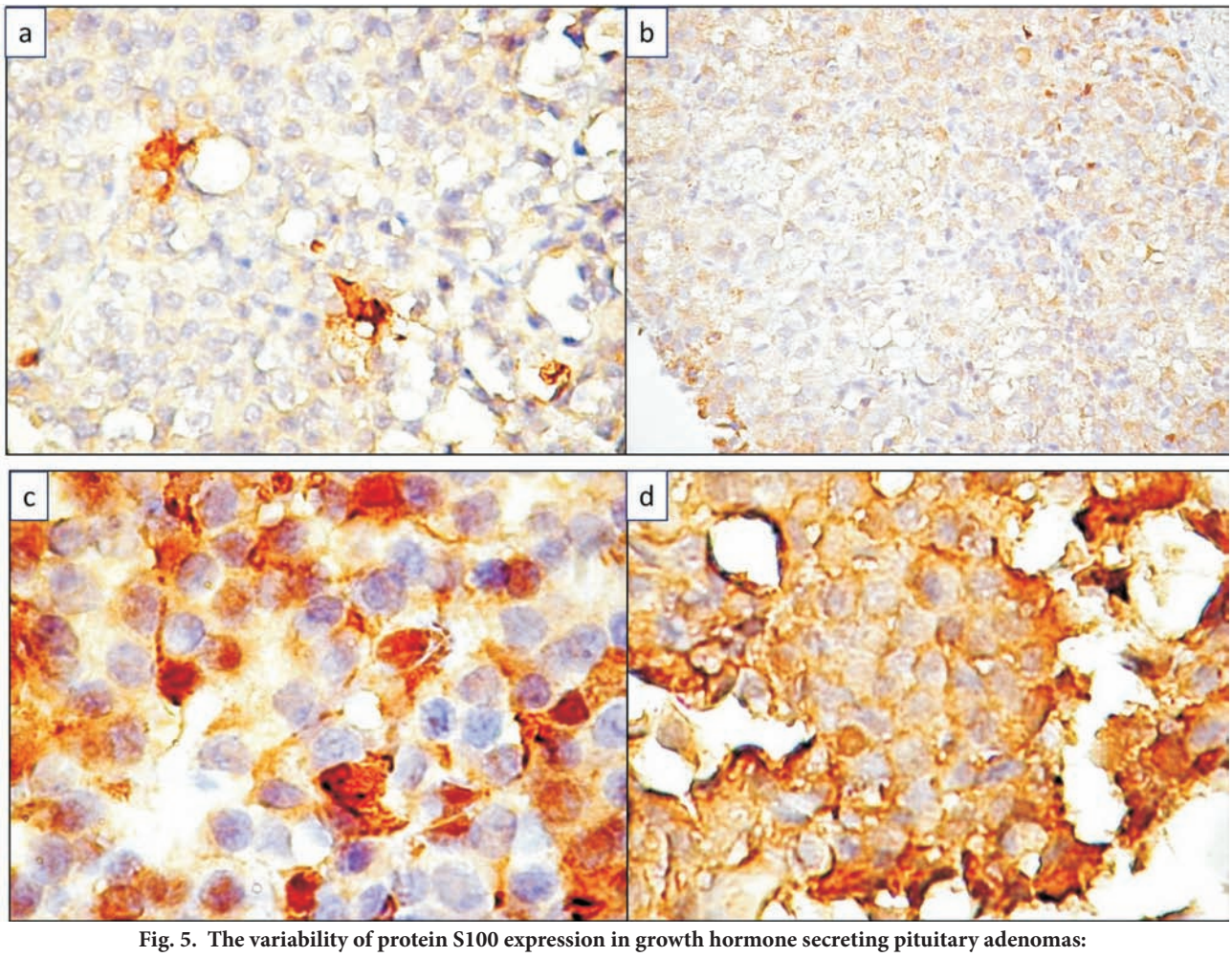

Fig. 5. The variability of protein S100 expression in growth hormone secreting pituitary adenomas: absent (a), low (b), intense, nuclear and cytoplasmic (c), intense, cytoplasmic (d).

hand, around the vascular spaces, S100 positive cells were distributed, having a nuclear and cytoplasmic expression, and morphology similar to that of stellate follicular cells. The expansions of the stellate follicular cells were strongly attached to the wall of the blood vessel, being also interconnected with one another (fig. 7a). These interconnections created a network of S100 positive expansions amongst which tumor cells were distributed. Focally, in the immediate vicinity of the S100 positive cells, tumor cells presented a low and inconstant reaction with a strict cytoplasmic distribution (fig. 7b).

As in the case of growth hormone secreting pituitary adenomas, the endothelial cells of the vessels located in the vicinity of the S100 positive cells had a positive reaction for protein S-100 with a nuclear distribution (fig. 7c). In the rest of

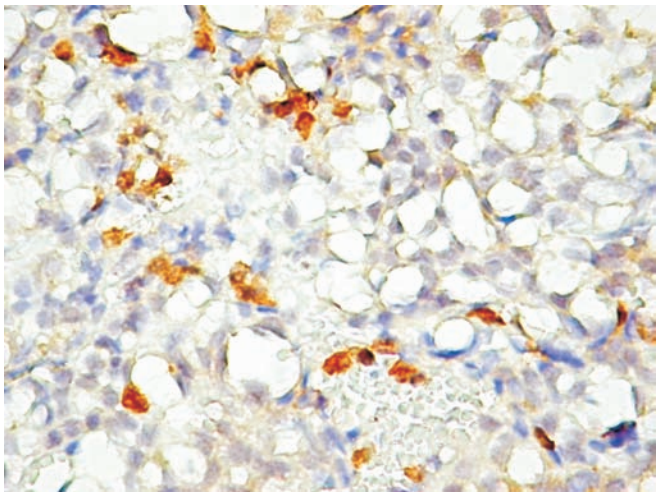

Fig. 6. Chromofobe type pituitary adenoma with chromofobe cells negative for protein S100 in their cytoplasm, with a focal and hetherogenous expression in the nuclei of the chromofobe cells and in the cytoplasm and the nucleus of stellate follicular cells inserted amongst chromofobe cells. In this case also, we may note the presence of endothelial cells that have a nuclear positive reaction for protein S100.

the tumor mass the S100 positive cells with a stellate follicular morphology were rarely encountered in adrenocorticotropic hormone (ACTH) secreting pituitary adenomas.

In relation to the hormone profile, none of the six markers used for immunohistochemical profiling significantly correlated from a statistical point of view with the expression of protein S100.

Discussion

Protein S100 expression was studied in pituitary adenomas, being frequently associated with stellate follicular cells [1, 2]. Their expression in tumor cells, separately quantified in various types of pituitary adenomas represents a sporadic subject in literature and, due to this reason; the correlations with the prognosis, long term survival, recurrences and therapeutic implications are extremely unconvincing at the time being. Increasing data suggest the capacity of tumor endocrine and non-endocrine cells to transdifferentiate themselves in stellate follicular cells where the two markers overlap in what is considered their immunohistochemical expression, these

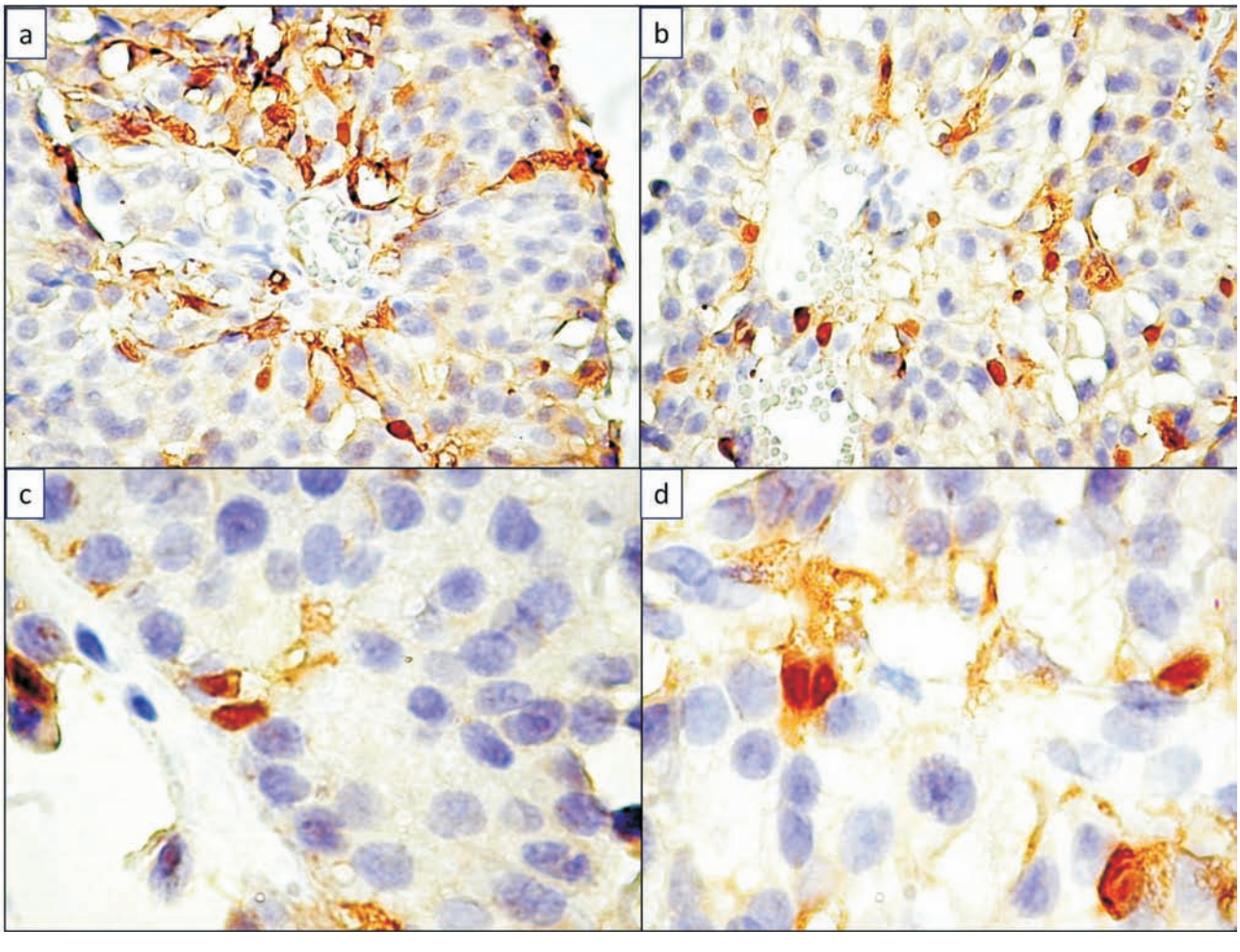

Fig. 7. Protein S100 is expressed in ACTH secreting pituitary adenomas. S100 positive cells, at a nuclear and cytoplasmic level, distributed in palisade around the blood vessels (a). These cells present numerous branched expansions, inserted amongst tumor cells, on the one hand and interconnected with one another forming networks (b, c). On occasion, S100 positive cells were observed as groups located amongst tumor cells that presented a low focal reaction for protein S100 (b, d).

FS cells actually being considered as pluripotent stem cells [3, 4]. The "retrodifferentiation" phenomenon was observed and described especially in case of ACTH secreting pituitary adenomas [4]. In our study we also observed a particular aspect of distribution, localization and S100 expression in case of ACTH secreting pituitary adenomas.

As a paradox, the description of protein S100 expression in the normal pituitary gland is restricted only at the evaluation of foliculostimulating hormone cells. We have not found any data in the literature regarding protein S100 expression, differentiated in the endocrine cells of the normal human pituitary gland. We observed a moderate immunohistochemical expression in the acidophilic, growth hormone secreting cells, and low in the chromofobe cells. The expression pattern also remained in case of growth hormone secreting pituitary adenomas where we noticed a variability of S100 expressions. This aspect was visible especially in case of mixed pituitary adenomas where the growth hormone secreting component was intensely positive for protein S100 while the basophilic component was negative or the chromofobe one was low positive for protein S100.

Conclusions

1. Protein S100 expressions in tumor cells is implicated in the pathogenesis of the growth hormone and prolactin secreting pituitary adenomas, the mechanisms of activation being nowadays incompletely studied. This aspect seems to represent an unfavorable prognostic factor that governs the retrodifferentiation phenomenon and supports the presence of pluripotent stem cells.

2. Through analogy with the observations obtained in other tumor types, it is possible that protein S100 pituitary adenomas to represent a group of pituitary adenomas with an aggressive behavior and a high capacity of invasion and recurrence, aspects that represent an unfavorable prognostic factor.

References

1. Inoue K, Couch EF, Takano K, Ogawa S. The structure and function of folliculo-stellate cells in the anterior pituitary gland. Arch Histol Cytol. 1999;62(3):205-18.
2. Devnath S, Inoue K. An insight to pituitary folliculo-stellate cells. J Neuroendocrinol. 2008;20(6):687-91.
3. Horvath E, Kovacs K. Folliculo-stellate cells of the human pituitary: a type of adult stem cell? Ultrastruct Pathol. 2002;26(4):219-28.
4. Min HS, Lee SJ, Kim SK, Park SH. Pituitary adenoma with rich folliculo-stellate cells and mucin-producing epithelia arising in a 2-year-old girl. Pathol Int. 2007;57(9):600-5.