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Pituitary adenoma-neuronal choristoma is a pituitary adenoma with ganglionic differentiation

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ABSTRACT

The presence of ganglion cells within an endocrine pituitary tumor has been named hamartoma, choristoma, gangliocytoma, or most recently pituitary adenoma-neuronal choristoma (PANCH). The presence of neuronal differentiation in regular pituitary adenomas has been previously suggested, however, its origin, the extent of its presence, and the relationship between the neuronal elements and the pituitary adenoma remain uncertain. Thus, to further explore the neuronal potential of pituitary tumors, we used immunohistochemistry on pituitary tumors of different grades, with a neuronal antigen protein (NeuN) antibody as a specific marker for mature neuronal differentiation. We found NeuN expression in 26.47% (9/34) cases of pituitary tumors without ganglionic differentiation (7 adenomas, 1 atypical adenoma and 1 pituitary carcinoma), in addition to NeuN expression in pituitary adenomas with ganglionic cells (2/2). Thus, neuronal expression is an innate property of pituitary adenomas. We propose that the rare presence of ganglionic cells in pituitary adenomas is not the result of a separate lesion or "collision sellar tumors", as previously suggested, but a ganglionic neuronal differentiation in an endocrine neoplasm. The ganglionic cells may be arising from uncommitted stem/progenitor cells that contain both neuronal and endocrine properties. A label of "pituitary adenoma with ganglionic differentiation" would better reflect the dual differentiation in a neuroendocrine tumor than the current label "PANCH".

1. Introduction

Adenohypophysis and neurohypophysis do not typically contain cells with morphological features of mature neuronal elements. However, the occasional presence of ganglionic elements within a pituitary tumor, although rare, has been recognized as early as 1926. The origin of ganglionic cells in an area that is otherwise devoid of native neuronal element has long puzzled pathologists. In addition, studies have demonstrated immunohistochemical evidence of neuronal expression in adenoma cells within mixed gangliocytoma and pituitary adenoma tumors, in both areas of neuronal and endocrine cells (Robertson et al., 1964; Saeger et al., 1994; Geddes et al., 2000; Johnson et al., 2007; Kurosaki et al., 2002; Thodou et al., 2004; Kontogeorgos et al., 2006; Rotondo et al., 2014; Koutourousiou et al., 2010; Saeger et al., 1997; Towfighi et al., 1996; Vidal et al., 2001). The markers for neuronal expressions reported in pituitary adenomas included NF, PNF, NeuN, class III tubulin, and Hu (Kontogeorgos et al. 2006; Horvath et al., 1994; Johnson et al. 2007). Multiple hypotheses were suggested regarding the origin of the neuronal elements within an adenoma: 1) Heterotopic hypothalamic tissue. 2) Neuronal metaplasia of the adenoma cells. 3) Originating in pleuripotential stem/progenitor cells within in the pituitary that have the capacity to give rise to pituitary adenoma with neuronal expression and have the ability to undergo full neuronal transformation (Thodou et al. 2004; Kotongoeros et al. 2006).

In this study, we investigated the neuronal expression in endocrine cells using neuronal-specific immunohistochemistry stains on 34 pituitary tumors of different grades (adenomas, atypical adenomas and carcinomas) in addition to 2 tumors with a combination of ganglionic and endocrine differentiation.

2. Materials and methods

The study was performed on 34 cases of pituitary tumors (adenoma, atypical adenoma, and carcinoma) from our institution, which were collected during the period of four years (2008–2012). Routine examination of the hematoxylin and eosin (H&E) stain from paraffin-embedded tissue, and immunohistochemistry stains including synaptophysin (SYN; monoclonal, DakoCytomation, dilution 1:20), adrenocortitrophic hormone (ACTH; monoclonal, Dako, dilution 1:75), follicle-stimulating hormone (FSH; monoclonal, BioGenex, dilution 1:200), luteal hormone (LH; monoclonal, Abcam, dilution 1:500), human growth hormone (hGH, monoclonal, BioGenex, dilution 1:100), thyroid-stimulating hormone (TSH, monoclonal, BioGenex, dilution 1:100), and proliferation index

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(Ki-67, monoclonal, Dako, dilution 1:150) were performed. Additionally, neuronal-specific immunohistochemistry stains were performed, including neuronal nuclei (NeuN, monoclonal, Millipore, dilution 1:100) and neurofilament (NF, monoclonal, DakoCytomation, and dilution 1:100) on all cases.

Immunohistochemistry stains that have been routinely utilized for the detection of neuronal structures include neuron specific enolase (NSE), chromogranin, NF, synaptophysin, and NeuN. However, it has been demonstrated that NSE is not specific for neuronal linage (Soylemezoglu et al. 2003; Wolf et al. 1996; Mullen et al. 1992); synaptophysin is a membrane glycoprotein which is localized in the presynaptic vesicles and therefore the immunoreactivity is diffused without consistent labeling of neuronal elements, and it also includes purely endocrine cells (Wolf et al. 1996; Sarnat et al. 1998; Lavezzi et al. 2013; Mullen et al. 1992); and NF, depending on their molecular weight and degree of phosphorylation, have highly variable immunoreactivity (Wolf et al. 1996); all of which make interpretation difficult.

A60 is a monoclonal antibody, which specifically recognizes the DNA-binding neuron-specific protein NeuN. Developmentally, NeuN expression occurs in association with terminal neuronal differentiation and is expressed in neurons that are at post-mitotic stage and/or in late stages of maturation but does not stain the nuclei of immature neuronal cells (Sarnat et al. 1998). Multiple studies have demonstrated that NeuN also does not have immunoreactivity in normal pituitary gland tissue (Wolf et al. 1996; Sarnat et al. 1998). These properties make NeuN the most sensitive and specific marker for mature neuronal element in pituitary tumor.

On histological and immunohistochemical basis 31 of the cases were diagnosed as pituitary adenomas, two were atypical pituitary adenomas (proliferation index ≥10%, one with proliferation index of 30%, likely to be carcinoma, but without metastases), and one case was a pituitary carcinoma with a metastasis to the liver. The remaining two cases were diagnosed as mixed pituitary adenoma and gangliocytoma (or pituitary adenoma-neuronal choristoma). The patient characteristics and clinical diagnoses were obtained through electronic medical record.

Table 1
Patients and tumor characteristics.

Case#	Age	Sex	ACTH	LH	FSH	hGH	TSH	PRL	Ki67	SYN	NF	NeuN
1	54	F	Neg	Pos	Pos	Neg	Neg	Neg	1%	Pos	Neg	Pos
2	40	M	Neg	Neg	Pos	Neg	Neg	Pos	5%	Pos	Neg	Pos
3	57	F	Pos	Neg	Neg	Neg	Neg	Neg	5%	Pos	Neg	Pos
4	43	M	Neg	Neg	Neg	Neg	Neg	Neg	5%	Pos	Neg	Pos
5	33	F	Neg	Neg	Neg	Neg	Neg	Neg	2%	Pos	Neg	Pos
6	55	F	Neg	Pos	Pos	Neg	Neg	Neg	1%	Pos	Neg	Pos
7	55	F	Pos	Neg	Neg	Neg	Neg	Neg	3%	Pos	Neg	Pos
8	70	F	Neg	Neg	Neg	Neg	Neg	Pos	30%	Pos	Neg	Pos
9	47	M	Pos	Neg	Neg	Neg	Neg	Neg	10%	Pos	Neg	Pos
10	47	M	Pos	Neg	Neg	Neg	Neg	Neg	7%	Pos	Neg	Neg
11	55	F	Pos	Neg	Neg	Neg	Neg	Neg	3%	Pos	Neg	Neg
12	59	F	Pos	Neg	Neg	Neg	Neg	Neg	3%	Pos	Neg	Neg
13	65	M	Neg	Pos	Pos	Neg	Neg	Neg	5%	Pos	Neg	Neg
14	45	F	Neg	Pos	Pos	Neg	Neg	Neg	5%	Pos	Neg	Neg
15	64	F	Neg	Neg	Pos	Neg	Neg	Neg	5%	Pos	Neg	Neg
16	63	F	Neg	Neg	Pos	Neg	Neg	Neg	5%	Pos	Neg	Neg
17	70	M	Neg	Neg	Pos	Neg	Neg	Neg	5%	Pos	Neg	Neg
18	69	F	Neg	Neg	Pos	Neg	Neg	Neg	2%	Pos	Neg	Neg
19	77	F	Neg	Neg	Neg	Pos	Neg	Pos	3%	Pos	Neg	Neg
20	60	F	Neg	Neg	Neg	Neg	Neg	Pos	5%	Pos	Neg	Neg
21	44	M	Neg	Neg	Neg	Neg	Neg	Pos	1%	Pos	Neg	Neg
22	31	F	Neg	Neg	Neg	Neg	Neg	Pos	5%	Pos	Neg	Neg
23	61	M	Neg	Neg	Neg	Neg	Neg	Neg	1%	Pos	Neg	Neg
24	52	F	Neg	Neg	Neg	Neg	Neg	Neg	1%	Pos	Neg	Neg
25	62	M	Neg	Neg	Neg	Neg	Neg	Neg	1%	Pos	Neg	Neg
26	41	F	Neg	Neg	Neg	Neg	Neg	Neg	5%	Pos	Neg	Neg
27	71	M	Neg	Neg	Neg	Neg	Neg	Neg	5%	Pos	Neg	Neg
28	34	M	Neg	Neg	Neg	Neg	Neg	Neg	3%	Pos	Neg	Neg
29	65	F	Neg	Neg	Neg	Neg	Neg	Neg	1%	Pos	Neg	Neg
30	41	M	Neg	Neg	Neg	Neg	Neg	Neg	5%	Pos	Neg	Neg
31	43	M	Neg	Neg	Neg	Neg	Neg	Neg	5%	Pos	Neg	Neg
32	64	M	Neg	Pos	Neg	Neg	Neg	Neg	1%	Pos	Neg	Neg
33	42	M	Neg	Pos	Pos	Neg	Neg	Neg	5%	Pos	Neg	Neg
34	54	F	Neg	Neg	Neg	Neg	Neg	Neg	10%	Pos	Pos	Neg
35[a]	43	F	Neg	Neg	Neg	Neg	Neg	Pos	0%	Pos	Pos	Pos
36[a]	32	F	Neg	Neg	Neg	Pos	Neg	Pos	15%	Pos	Pos	Pos

[a] Patients with mixed pituitary adenoma and ganglion cells; control cases. The remaining patients are diagnosed with pituitary adenoma or carcinoma.

3. Results

Patients' characteristics, diagnosis, and clinical presentation are summarized in Table 1. On H&E stain, the pituitary adenomas were composed of nested, monomorphic population of typical small to medium cells with slightly irregular round to oval nuclei, and delicate stippled chromatin. No ganglionic characteristic cells, with features including polyhedral large cells with enlarged nuclei and prominent nucleoli were present in the 34 cases of pituitary adenoma and carcinoma (Fig. 1A).

All 31 cases of pituitary adenoma, one case of atypical pituitary adenoma, and two cases of pituitary carcinoma demonstrated diffuse positivity for synaptophysin, variable staining of hormonal markers, consistent with the diagnosis of pituitary adenoma. All 34 cases were negative for NF stain. Nine of 34 (26.47%) cases showed variable nuclear staining for NeuN ranging from 5% of the adenoma cells in one case and up to 90% in one case (Fig. 1D). Light microscopy of the H&E stain showed no histologically distinctive features between the adenoma cells that are immunoreactive for NeuN compared to those that were not immunoreactive.

The two cases of mixed pituitary adenoma and gangliocytoma (patient #35 and patient #36) showed two distinct mixed populations of cells. One population, being the adenomatous component, consisted of monomorphic slightly irregular small to medium oval cells with delicate chromatin. The other population of tumor cells, corresponding to the gangliocytoma, consisted of large polyhedral mature ganglion cells, with abundant eosinophilic cytoplasm, round nuclei, and prominent nucleoli. The two distinct populations of tumor cells were intermixed (Fig. 2A). Immunohistochemistry stains further differentiated the two cell populations. The cells corresponding to ganglion cells histologically were strongly positive for NF and NeuN (Fig. 2C and D). A fraction of the adenomatous cells (~30%) was also positive for NeuN and few cells (<20%) were positive for NF. In addition, the stroma surrounding the ganglionic cells and adenoma cells was also positive for NF, likely representing neuropil. Both tumors were diffusely positive for synaptophysin (Fig. 2B).

Of the nine cases that demonstrated positive neuronal-like differentiation by NeuN staining, there was one with mixed FSH and GH hormonal staining, one with mixed GH and PRL hormonal staining, one prolactinoma, three corticotroph adenomas, and three null cell adenomas. All of the nine patients presented with clinical features related to endocrine abnormalities, most commonly with elevated ACTH level followed by elevated PRL.

4. Discussion

The presence of NeuN immunoreactivity in different grades of pituitary tumors including adenomas, atypical adenomas and carcinomas has not been previously reported and further provides support for neuronal expression of pituitary tumors which was seen in approximately one third of the cases in our case series. The fact that neuronal expression, as highlighted by NeuN immunoreactivity, occurs at such a high prevalence in our study population may represent an innate property of the endocrine neoplasm, and not a separate pathologic process. The findings of the case series presented here support the theory that endocrine neoplastic cells, in this case pituitary adenoma, contain neuronal elements that are much more common than previously observed.