Acta Neuropathol (2006) 111: 46–52
DOI 10.1007/s00401-005-1111-8

CASE REPORT

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Morphologic changes of prolactin-producing pituitary adenomas after short treatment with dopamine agonists

Received: 14 June 2005 / Revised: 13 September 2005 / Accepted: 14 September 2005 / Published online: 23 November 2005

Abstract Treatment of patients with prolactin (PRL)-producing pituitary adenomas with dopamine agonists has proved successful for most cases. Dopamine agonists inhibit PRL secretion, suppress cell proliferation, and may induce apoptosis to adenoma cells. Dopamine agonists induce striking morphologic changes in the majority of treated PRL-producing adenomas. To date, these morphologic effects have been primarily described only after long-term treatment. To the best of our knowledge, no similar studies have investigated apoptotic alterations induced after short-term therapy. The purpose of this report is to describe the morphologic changes seen in PRL-producing adenomas after short-term dopamine agonist treatment. We present two cases of PRL-producing macroadenomas, both from male patients who received treatment with dopamine agonists, the first for 5 and the second for 8 days. In contrast to long-term treatment, no striking reduction of PRL immunoreactivity was noted. Slight stromal fibrosis was noted in case 1, which contained several cells all in late phase of apoptosis. In addition to typical apoptotic cells, numerous ''dark'' cells representing another common form of cell death were also noted. These novel findings represent characteristic features of short-term dopamine agonist treatment, which are not seen in long-term treatment.

Keywords Apoptosis · Bromocriptine · Ki-67 · MIB-1 · Prolactinoma

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Introduction

Normalization of hormone levels in functioning adenomas and elimination or reduction of mass effects represents major objectives of medical treatment of pituitary adenomas. Dopamine agonists have long been successfully used in the treatment of patients with prolactin (PRL)-producing adenomas, with their effectiveness approaching 90% [6]. They (a) inhibit PRL gene transcription, PRL synthesis, and release [19, 27, 31, 33], (b) suppress cellular proliferation [8, 18, 25], and (c) induce apoptosis [14]. As a result, lowering of serum PRL levels, improvement of clinical symptoms and reduction of tumor size are achieved [4, 5, 10, 26]. Although clinical symptoms reappear after discontinuation of treatment, some adenomas do not regrow. Although a rare occurrence, complete cure may result from pituitary apoplexy in patients on dopamine agonists [1]. The effects of these agents are mediated through membrane receptors, mostly of the dopamine 2 (D_2) receptor type. Several ergot and nonergot derivatives, such as long-acting oral and injectable quinagolide, which also targets the D_2 receptor, were developed during the last decade. They appear to be more effective inhibitors of PRL secretion and are better tolerated than bromocriptine [7, 28, 32, 33]. Resistance to dopamine agonists may be seen and is attributed to loss of D_2 receptors from PRL-producing adenoma cells [22]. Despite the presence of D_2 receptors in adenoma types, other than those engaged in PRL production, treatment with dopamine agonists has proven ineffective in these cases [29].

Dopamine agonists induce striking morphologic changes in the majority of treated PRL-producing adenomas. These morphologic effects have been described

after long-term treatment. A single in vitro study has reported by electron microscopy "necrobiotic phenomena" in PRL-producing adenomas after short treatment with a dopamine agonist [23]. To the best of our knowledge, no similar studies describing the spectrum of apoptotic changes induced after short-term treatment of patients with PRL-producing adenomas have been published.

The purpose of this report is to present the histologic, histochemical, immunohistochemical, and ultrastructural alterations induced by short-term dopamine agonist treatment of patients with PRL-producing adenomas.

Case reports

Case 1

A 48-year-old man presented with loss of vision in the right eye over a period of 8 months. During the past 3 months, he started having morning headaches. CT scan and MRI demonstrated a very large, highly vascularized pituitary adenoma measuring 3.1×2.8×2.9 cm. It showed direct extension into the sphenoid sinus and considerable bony erosion of the sellar floor and petrous apices. In addition, the tumor showed suprasellar extension, compression of the right optic nerve, and unilateral deviation of the chiasm. The mass had a posterosuperior cystic element. The serum PRL level was significantly elevated at 1,435 μg/l (normal < 5 μg/l). The patient underwent clinical examination and investigation, which showed no loss of libido, and his serum testosterone level was low normal. The patient was put on therapy with dopamine agonists (bromocriptine); he, at first, received 2.5 mg daily for 2 days and then 5.0 mg daily for 3 more days. At that time, he noticed slight improvement in right-sided vision. Nonetheless, marked right temporal hemianopsia and a large centrocecal scotoma persisted. His vision was reduced to 20/80. The patient was advised to undergo immediate surgical decompression by transsphenoidal hypophysectomy and the tumor was partly removed. On the day of operation his serum PRL levels dropped to 409 μg/l and after 1 month to 16.2 μg/l (Table 1).

Case 2

A 21-year-old man presented with complete blindness in his left eye and near total blindness on the right. He complained of headaches during the last 5 months. CT and MRI scans showed a contrast enhancing macroadenoma measuring 5 cm at greatest diameter. The tumor expanded and eroded the sella and sphenoid sinus, and completely obliterated the anterior third ventricle. His serum PRL level was found to be 7,650 μg/l. He was immediately started on 10 mg bromocriptine a day, for a total of 8 days. Although his vision in the formerly blind left eye improved over the next 4 days, the marked bitemporal hemianopsia and amblyopia in the left eye remained unchanged. Clinical examination showed evidence of hypopituitarism. Transsphenoidal surgery was then undertaken and the tumor was partly removed. His serum PRL levels decreased to 409 μg/l on the day of operation and gradually diminished to 10.2 μg/l after 13 days (Table 1).

Table 1 Serum prolactin levels of patients before operation (*Pre-op*), the day of operation (*Op day*) and the following post operation days (*Post-op*), expressed in μg/l

	Case 1	Case 2
Pre-op	1,435	7,650
Op day	409	493
Post-op 1	65	192
Post-op 2	86	
Post-op 3	103	
Post op 6		66
Post op 13		10.2
Post-op 30	16.2	

Morphologic methods

For light microscopy, 4- to 6-μm sections of formalin-fixed and paraffin-embedded tissues were stained by the hematoxylin and eosin and the periodic acid-Schiff (PAS) methods. For immunohistochemistry, the standard avidin-biotin-peroxidase complex (ABC) technique was utilized. Antibodies directed against the full spectrum of adenohypophysial hormones were used: Growth hormone (GH, 1:4,000), PRL (1:3,000), adrenocorticotropin (ACTH, 1:2,500), β-thyroid stimulating hormone (β-TSH, 1:2,000), ß-follicle stimulating hormone (β-FSH, 1:1,500), β-luteinizing hormone (β-LH, 1:2,000) and α-subunit of glycoprotein hormones (α-SU, 1:1,500). All pituitary hormone antibodies were provided from the National Hormone and Pituitary Program (NHPP; Torrance, CA). Pretreatment of sections with 1 mg/100 ml pronase (Sigma, St. Louis, MO) was performed in room temperature. Additional antibodies used included CD68 (clone KP1, 1:600, Dako, Glostrup Denmark) and caspase-3 (1:200, Biocare Medical, Walnut Creek, CA). Tumor cell proliferation was estimated using the Ki-67 antibody (clone MIB-1, 1:50, Novacastra Labs, Newcastle upon Tyne, UK). Before the application of the latter antibody, sections were incubated in sodium citrate buffer, pH 6.0 in a pressure cooker for 2 min. The apoptotic labeling index was assessed by the TUNEL technique as described previously [16]. For ultrastructural study, fresh tissue was fixed in 4% glutaraldehyde, routinely processed, and examined on a Philips 410LS transmission electron microscope.

Results

Case 1

By histology, the very cellular, slightly acidophilic, PAS-negative pituitary adenoma featured small cells

with slightly to moderately pleomorphic, markedly hyperchromatic nuclei, and a rim of scant cytoplasm. Scattered mitotic figures were seen. In a few areas of the tumor, many adenoma cells were seen to show late apoptotic nuclear changes (Fig. 1a). Apoptotic cells appeared to "float" due to their complete loss of connection with adjacent cells, showed compact acidophilic cytoplasm, and contained apoptotic bodies. Immunohistochemistry for PRL showed strong paranuclear (Golgi zone) reactivity. Most adenoma cells with apoptotic changes retained their PRL immunoreactivity (Fig. 1b). Immunostains were negative for all other adenohypophysial hormones (GH, ACTH, β-LH, β-FSH, and β-TSH, α-SU). It is of note that vessels were often surrounded by PAS-positive and CD68-immunoreactive macrophages (Fig. 1c). In addition, in the areas showing brisk apoptotic activity, some PRL-positive cells, also immunoreactive for CD68, were found within the lumens of dilated sinusoids (Fig. 1d). The overall apoptotic labeling index was approximately 1.7%, and 2.3% of cells were caspase-3 positive (Fig. 1e, f). The Ki-67 proliferation index was high, exceeding 15% in some areas (Fig. 2). Therefore, this tumor should be designated "atypical adenoma".

By electron microscopy, a sparsely granulated adenoma was identified. The nuclear/cytoplasmic ratio was markedly increased. The irregular nuclei contained a fair amount of heterochromatic and prominent nucleolus. The quantitatively reduced cytoplasm contained tightly packed rough endoplasmic reticulum (RER) and Golgi membranes. The secretory granules measured 150–300 nm and were mostly distributed in the periphery of the cell. Throughout the specimen, practically all tumor cells displayed variable, but consistently higher than normal electron density. The neighboring tumor cells, usually seen in close juxtaposition in untreated PRL-producing adenomas were only focally apposed. Expansion of the intercellular space was the result of shrinkage of the cytoplasm (Fig. 3a). Several structures resembling apoptotic bodies were present, but most did not have the highly characteristic nuclear "capping" of chromatin. Instead, they contained large, electron-dense lumps of free-floating nuclear material, indicating that they represented cells undergoing division (Fig. 3b). Thus, it appears that most if not all dividing cells were eliminated by "programmed cell death." Cytoplasmic organelles also showed regressive changes. Although, at the light microscopic level, the tumor showed enhanced mitotic activity, electron microscopy showed no intact examples of mitosis.

Case 2

Histologic examination showed a cellular, chromophobic, PAS-negative pituitary adenoma with slight interstitial fibrosis. The tumor cells had scant cytoplasm. Nuclei exhibited mild pleomorphism and rare mitoses. Immunoreactivity for PRL was extensive and strong with a paranuclear distribution corresponding to the Golgi area. The Ki-67 proliferation index was low ($< 1\%$). No typical apoptotic cells were identified. By the TUNEL method, the apoptotic index was 0.14% and 0.40% of the cells were caspase-3 positive.

By electron microscopy, the adenoma was composed of closely apposed, small, round to elongate cells. Nuclei were ovoid, often multiple indented with a small nucleolus and moderate to large amounts of heterochromatin. The cytoplasm contained a modest amount of slightly dilated RER. The Golgi complexes were small and inactive with collapsed sacculi containing few developing secretory granules. In the rest of cytoplasm, secretory granules measured 100–200 nm. Granule extrusions were observed. In this specimen, the presence of "dark" cells was conspicuous (Fig. 3c, d). The gradual increase of electron density of the cells and dilatation of membranous organelles reflected loss of water content and cytoplasmic volume, the equivalent of cellular senescence. In the final phase, organelles became simply a shrunken remnant. The process did not involve changes in the nuclear morphology.

Discussion

Several studies during the last two decades have described the dramatic morphologic changes taking place in PRL-producing adenomas after treatment with dopamine agonists. By light microscopy, the tumors often appear hypercellular due to significant cell shrinkage. The cells undergo a remarkable reduction in cytoplasmic volume, nuclear hyperchromasia, and an increase in nuclear/cytoplasmic ratio. Long-term treatment leads to the development of extensive perivascular and interstitial fibrosis. Some tumors show reduced immunoreactivity for PRL [2, 3, 15, 17, 27]. Electron microscopy demonstrates marked reduction of RER and Golgi complex volumes [2, 3, 15, 27]. Nuclear abnormalities and cytoplasmic changes were observed in both tumors of the present study. A slight perivascular fibrosis was noted only in the second tumor; although it was treated with dopamine agonists for a longer period of time and at a somewhat higher dose, the stromal changes may be a reflection of longer growth and greater tumor size.

Previous studies have documented the occurrence of apoptosis in human pituitary adenomas, including PRL-producing tumors [14, 16]. The full morphologic spectrum of apoptotic events in pituitary adenomas was recently reviewed in detail by histology and electron microscopy [12].

According to the study of Vidal et al. [30], a form of cell death process distinct from apoptosis is encountered mainly in dopamine-treated PRL-producing adenomas. Progressively increasing cytoplasmic density represents its most striking morphologic feature. The cells appear "dark," both in terms of cytoplasm and nuclei. Unlike in apoptosis, no nuclear fragmentation is observed, even in

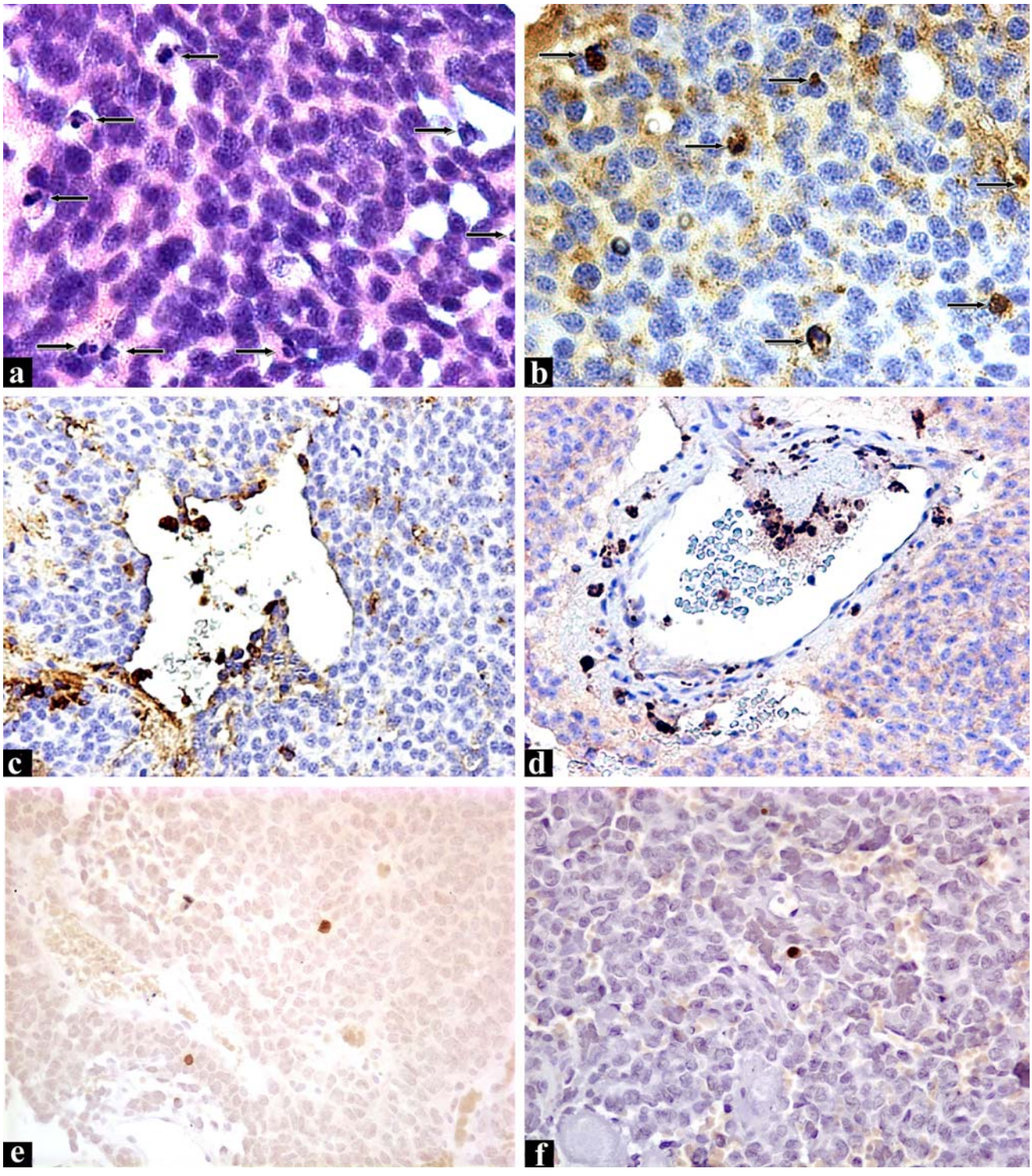

Fig. 1 **a** The chromophobic pituitary adenoma shows many apoptotic cells with apoptotic bodies (*arrows*) typical for late apoptotic changes; hematoxylin and eosin staining. **b** Apoptotic cells (*arrows*) are strongly reactive for PRL with paranuclear localization of the chromogen in some of them. Note that chromogen partly obscures the characteristic nuclear changes of apoptotic cells; ABC staining. **c** PRL-immunopositive cells and PRL-labeled remnants of apoptotic material around and within a sinusoidal lumen; ABC staining. **d** CD68-positive macrophages around and within sinusoids, probably phagocytozing remnants of apoptotic material; ABC staining. **e** TUNEL reaction in a pituitary adenoma showing a positive cell undergoing apoptosis with *brown* nuclear staining; TUNEL staining. **f** Caspase-3 immunostaining in a pituitary adenoma showing two positive cells with cytoplasmic staining; ABC staining. **a**, **b** ×160; **c**–**f** ×100

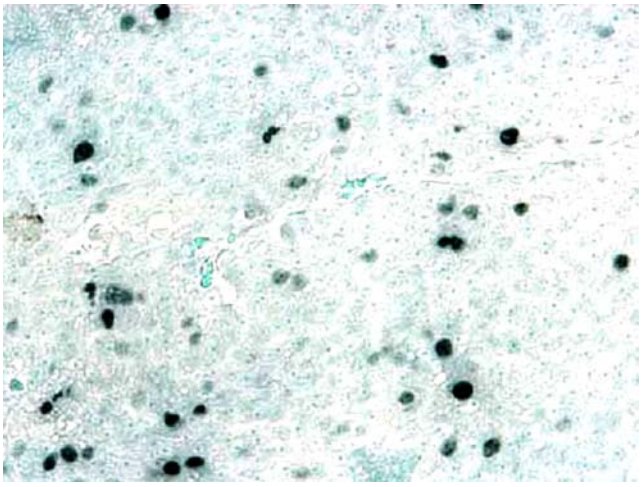

Fig. 2 High Ki-67 proliferation index exceeding 15%; ABC staining. ×100

advanced phases. Subsequently, extensive cytoplasmic vacuolization is noted. ''Dark'' and apoptotic cells can be observed concurrently in the same tissue section [30].

Although apoptotic indices generally differ between bromocriptine-treated and untreated human PRL cell adenomas, [14, 16], the changes are not uniformly seen. For example, in one study, a higher apoptotic index was shown in untreated PRL-producing adenomas as compared to bromocriptine-treated cases [14]. In another study, the apoptotic index was not found to be significantly higher in PRL-producing adenomas treated with dopamine agonist as compared with the untreated ones [24]. In contrast, however, mitotic counts and Ki-67 proliferation indices were significantly lower, particularly in cases treated with quinagolide as compared to untreated adenomas [25]. Other studies also reported lower proliferative activity in tumors treated by bromocriptine [8]. Some of these varied results may be explained by differences in the type of drug used, daily

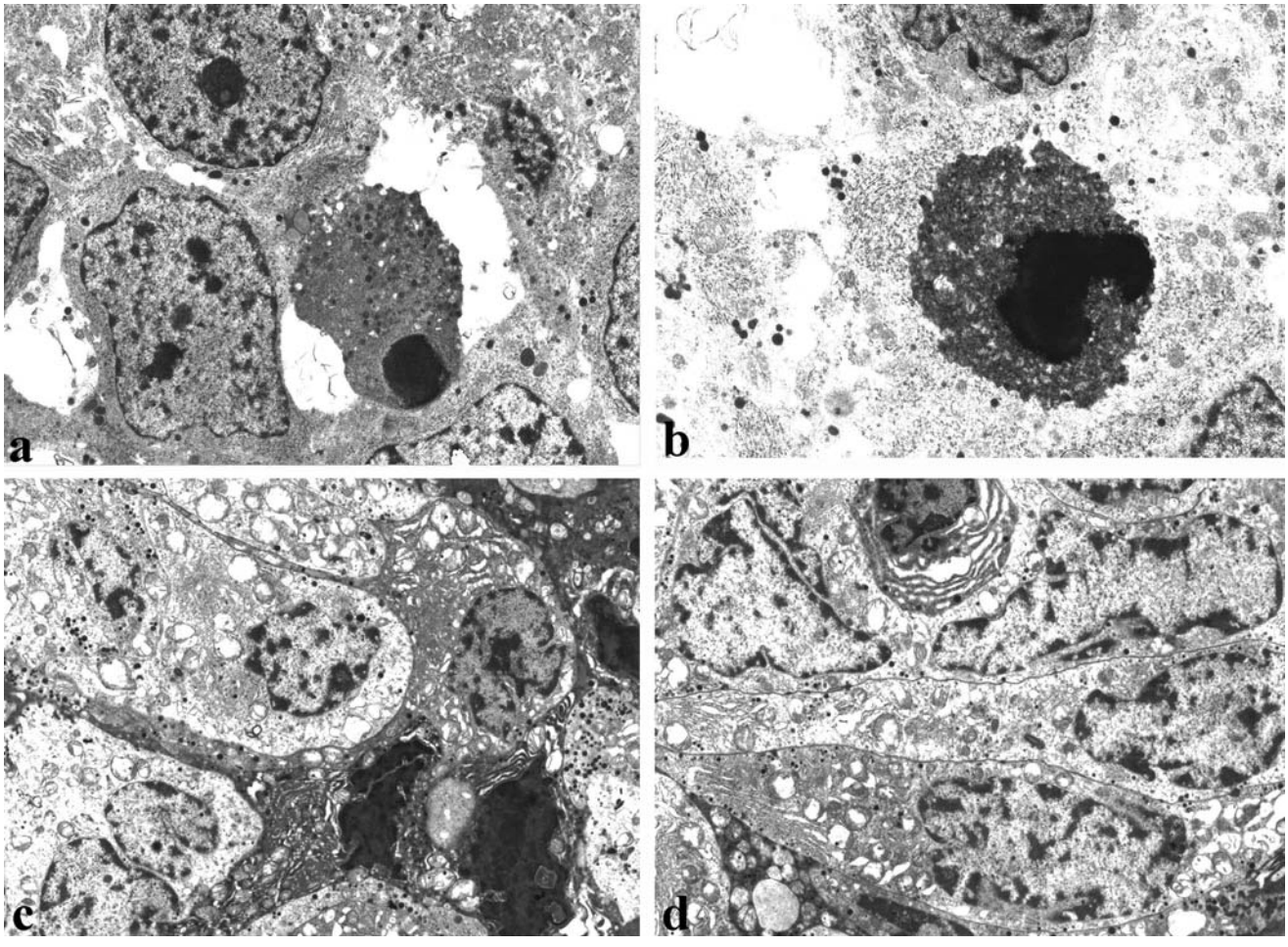

Fig. 3 a The small, variably dense cytoplasm of tumor cells appear somewhat compacted. Note the uneven widening of intracellular spaces and portion of apoptotic cell in the center. **b** Electron micrograph depicting an apoptotic body containing an irregularly outlined amorphous lump of nuclear substance, taken by variable tumor cell. **c** In this field, every adenoma cell of normal density is surrounded by the cell body of cytoplasmic process of variably dark cells. **d** Only two of the elongated tumor cells have normal electron density; the others display variable degrees of darkening. **a** ×9,000; **b** ×13,200; **c**, **d** ×6,300

dose, duration of treatment, and degree of cellular responsiveness to dopamine agonists [25].

Cell proliferation and apoptosis are essentially opposed physical phenomena, which, under normal conditions, maintain an optimal balance of cell numbers in the body. In neoplasia, mitoses and apoptosis are both up-regulated, but the balance is altered in favor of mitoses and resultant tumor progression. Not surprisingly, selective suppression of proliferation and/or induction of apoptosis represents the most important goal of drug therapy.

By light microscopy, brisk apoptotic activity was observed focally in only our first case. The PRL-positive cells found within the sinusoid lumens, probably representing remnants of apoptotic adenoma cells phagocytozed by CD68-positive macrophages. The presence of numerous PAS-positive macrophages surrounding tumoral vessels in this case may reflect activation of phagocytic mechanisms for rapid elimination of apoptotic cells. Apoptotic bodies are regularly taken up by macrophages and, to a lesser extent, adjacent neoplastic cells. According to previous studies, the occurrence of apoptosis in treated, compared to non-treated adenomas, is low, and therefore, it is difficult to identify their presence by histology alone, unless in situ end labeling techniques are employed [14, 24]. In our experience, once apoptotic cells can be identified by histology alone, various phases of the apoptotic sequence are usually seen. Interestingly, in our case 1, all apoptotic cells appeared to be in the same stage of the process.

Proper progression through cell cycle is controlled by a series of ''checkpoints'', where feedback signals can arrest advance into a new phase of cell cycle until the dividing cells have successfully completed the previous one [21]. The DNA mismatch repair system maintains genomic instability by detecting and correcting DNA mismatches generated during replication [11]. DNA mismatch repair is also involved in cell cycle checkpoint regulation, and apoptosis and its cell status can influence its response to a wide variety of therapeutic agents [20].

The apoptotic pathway relies on activation of caspases, a large family of highly conserved cysteine proteases. Caspase-dependent effectors cause chromatin condensation and nuclear DNA fragmentation, a morphologic change characteristic of apoptosis [9].

Due to the ephemeral nature of apoptosis as well as small sample size, apoptotic cells are rarely seen ultrastructurally in pituitary adenomas. Thus, as well documented in our case 1, the finding of multiple examples of apoptosis is consistently associated with aggressive growth, enhanced mitotic activity and caspase-3 activation. It was an intriguing ultrastructural finding that many dividing cells in the specimen seemed to undergo apoptosis. This interesting phenomenon suggests the selectivity of programmed cell death involving chiefly cells being in the cell cycle rather than those in interphase. This finding also implies that the cellular response to bromocriptine at the level of transcription may create conditions incompatible with the successful completion of cell division.

As opposed to the sporadic occurrence of apoptosis in PRL-cell adenomas, the conspicuous presence of ''dark cells'' is a general finding in chronically treated dopamine agonist-responsive tumors. In case 1, treated only for 5 days with bromocriptine, an increased density of cytoplasm was evident in many cells, but no typical dark cells had yet occurred. In the tumor of case 2, treated for 8 days at higher doses, the prominence of dark cells was readily apparent. The dark cell phenomenon is the ultrastructural manifestation of the universal form of cell death. Before having completed their last division, differentiated cells are programmed to enter a phase of senescence characterized by gradual loss of water, increase of electron density, and significant shrinkage [30]. The process is unrelated to other forms of cell death; unlike apoptosis, the nuclear morphology remains unchanged and unlike cell necrosis, the cell membrane is intact.

In that our first patient was treated with 2.5 mg and 5.0 mg bromocriptine daily for 2 and 3 days, respectively, and the second patient received 10 mg bromocriptine daily for 8 days (i.e., a fourfold higher daily dose for the first 2 days and a twofold higher for the next 6 days) this may reinforce the concept that a subset of adenoma cell population is more prone to die by undergoing dramatic apoptotic changes in early phase of treatment with dopamine agonists to explain the time differing and dose-dependent changes in response to apoptotic induction [13, 14].

In summary, it is known that the apoptotic process lasts for a short period of time; as a result, rapid elimination of this susceptible cell population may explain the scarcity or even absence of apoptotic cells in adenoma tissue from patients receiving long-term dopamine agonist treatment. In contrast to apoptosis, a rapid event, ''dark'' cell death might last for a longer period of time and be more readily evident. These two cases, although few, provide us with novel information regarding the morphologic response to short-term dopamine agonist treatment of PRL-producing adenomas and the occurrence of two forms of cell death involved in the process. Further studies are needed to answer lingering questions.

Acknowledgments This study was supported in part by the generous donation of Mr. and Mrs. Jarislowski, and the Lloyd Carr Harris Foundation (to K. Kovacs). The authors are indebted to the National Hormone and Pituitary Program (NHPP; Torrance, CA) for providing the pituitary hormone antibodies. We also thank Mrs. Magda Pateraki for technical assistance and Mrs. Dee Chase for excellent secretarial support.

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