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Oncocytomas and null cell adenomas of the human pituitary: morphometric and in vitro functional comparison

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Summary. In this study, light microscopic and ultrastructural morphometric features of oncocytomas and null cell adenomas were compared and the morphometric data were correlated with in vitro endocrine activity. All tumours were unassociated with clinical or biochemical evidence of hormone excess and were diagnosed as oncocytomas or null cell adenomas, using histology, immunohistochemistry and electron microscopy. In oncocytomas, when compared with null cell adenomas, light microscopic morphometry revealed that total cell areas were significantly larger and nuclear cytoplasmic ratios were smaller due to an increase in cytoplasmic areas. Ultrastructural morphometry disclosed an abundance of mitochondria in oncocytomas. Absolute volumes of cytoplasmic organelles per cell were not reduced in oncocytomas compared with those of null cell adenomas. These results indicate that accumulating mitochondria do not replace other cytoplasmic organelles, and furthermore that the functional potential of oncocytomas is not lost. In vitro study demonstrated the production of pituitary hormones, primarily gonadotropins in oncocytomas and null cell adenomas. It can be concluded that oncocytomas, which represent the final stage of oncocytic transformation, have a close relationship with null cell adenomas based on morphometric comparison as well as in vitro studies.

Key words: Electron microscopy – Morphometry – Null cell adenoma – Oncocytoma – Pituitary adenoma

Introduction

Oncocytomas are tumours composed of oncocytes, cells which are characterized by an abundance of cytoplasmic mitochondria. The term "oncocyte" was first applied by Hamperl (1931) after the Greek word "onkousthai" which means to swell, to become larger. Jaffé (1932) introduced the name "oncocytoma" for tumours composed entirely of these cells. Such tomours are usually benign and arise in various organs, such as salivary glands, thyroid, parathyroid, kidney, etc. Pituitary oncocytomas were first described in 1973 (Kovacs and Horvath 1973; Landolt and Oswald 1973). Subsequently, there have been a number of reports of oncocytomas occurring in the pituitary gland (Kovacs et al. 1974; Saeger 1975; Bauserman et al. 1978; Gjerris et al. 1978; Roy 1978; Kalyanaraman et al. 1980).

The term null cell adenoma was first introduced by Kovacs et al. (1980) to designate pituitary adenomas which lacked histological, immunohistological or ultrastructural markers that would allow the recognition of their cytogenesis.

Pituitary oncocytomas and null cell adenomas have been considered to be endocrinologically inactive, since they are unassociated with clinical or biochemical evidence of adenohypophysial hormone excess. They have been well documented in the literature with detailed reports of their light microscopic and electron microscopic features (Saeger 1975; Bauserman et al. 1978; Roy 1978; Goebel et al. 1980; Jalalah et al. 1985; Kovacs and Horvath 1986; Martinez 1986). Because of similarities in epidemiological and clinical features as well as a morphological overlap, oncocytomas are regarded as variants of null cell adenomas (Scheithauer 1984; Kovacs and Horvath 1986, 1987). Recently, these adenomas have received considerable attention from the functional point of view (Klibanski 1987); in vitro studies, documenting hormone release into culture media, have demonstrated that these adenomas, which have been believed to be hormonally nonfunctioning, can produce some hormones, primarily glycoprotein hormones (Lipson et al. 1978; Mashiter et al. 1981;

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Surmont et al. 1983; Asa et al. 1986). However, morphometric study with statistical analysis, which is a precise and quantitative method to demonstrate minute changes in cell components, has not been performed and morphological parameters and endocrine activity have not been correlated.

This study was undertaken to compare the light microscopic and ultrastructural morphometry of oncocytomas and null cell adenomas, and to correlate these morphometric data with in vitro hormone secretion.

Materials and methods

Ten oncocytomas and 10 null cell adenomas were sampled randomly from a collection of more than 1500 surgically-removed pituitary adenomas. All cases were unassociated with clinical or biochemical evidence of hormone excess and were diagnosed by histology, immunohistochemistry and electron microscopy. The details of immunohistochemical procedures and the criteria applied for diagnosis have been described in previous papers (Asa et al. 1986). There is still controversy about the definition of oncocytomas. Some authors (Landolt et al. 1978; Saeger 1984) diagnose oncocytomas when 50% or more of adenoma cells show oncocytic transformation. Others, however, (Kovacs and Horvath 1986) claim that almost all cells should be oncocytes for the diagnosis of oncocytoma and tumours in various stages of oncocytic transformation should be named according to their cellular derivation. In this study, the term oncocytoma is restricted to adenomas in which almost all cells have features of oncocytes. It should be mentioned that in null cell adenomas, cells exhibiting variable degrees of oncocytic change are often encountered; such cells were excluded from this study.

The morphometric study consisted of 2 parts: light microscopic morphometry and ultrastructural morphometry for cytoplasmic organelles and mitochondrial subcompartments. Pieces of adenoma tissue were fixed in 2.5% glutaraldehyde in Sorensen's buffer, postfixed in 1% osmium tetroxide in Millonig's buffer, dehydrated in a graded series of ethanol, processed through propylene oxide and embedded in an Epon-Araldite mixture. Two blocks were studied from each case.

For light microscopic morphometry, 250 cells from each of 2 blocks, a total of 500 cells of each case, were measured on toluidine-blue stained semi-thin sections at a magnification of 1000 using a Leitz ASM digital image analyzer. Cell and nuclear areas were measured and the cytoplasmic area and nuclear/cytoplasmic ratios were calculated. For ultrastructural morphometry, sections from 2 blocks of each case were stained with uranyl acetate and lead citrate and investigated with a Philips 410 LS electron microscope.

To study the morphometry of cytoplasmic organelles in each case, 10 photographs from each of two blocks (total 20 photographs) were taken with a constant primary magnification of 4400. Final photographic magnification was 11440. In order to collect photographic material in an unbiased way, electron micrographs were taken at random areas located in the corners of grid spaces, as suggested by Weibel et al. (Weibel et al. 1966; Weibel 1969).

The following parameters were determined: 1) Cytoplasmic volume density of mitochondria; 2) cytoplasmic volume density of endoplasmic reticulum; 3) cytoplasmic volume density of Golgi apparatus; 4) cytoplasmic volume density of lysosomes; 5) cytoplasmic volume density of secretory granules; 6) surface density of mitochondria and ratio of mitochondrial surface area to unit mitochondrial volume; 7) diameter of secretory granules (25 secretory granules per photograph, total 500 from each case); 8) area of mitochondria (25 mitochondria per photograph, total 500 from each case).

Ultrastructural morphometry of mitochondrial subcompartments, other than the parameters mentioned above, was performed as well. Measurements, as described by other authors (Smith and Page 1976; Cieciura et al. 1986), were obtained from mitochondria in which the largest areas of cristae were transversely cut. Twenty electron micrographs from each case were taken randomly at a primary magnification of 56800 (final: 142480) and 20 *mitochondrial profiles* from each case were studied. The following parameters were assessed: 1) volume density of matrix compartment per unit mitochondrial volume; 2) volume density of intracristal compartment including most inner membrane (cristal membrane) per unit mitochondrial volume; 3) volume density of inner membrane per unit mitochondrial volume; 4) volume density of outer compartment per unit mitochondrial volume; 5) volume density of outer membrane per unit mitochondrial volume; 6) surface density of inner and cristal membrane per unit mitochondrial volume.

In this study, ultrastructural morphometry was restricted to cells with no evidence of damaged plasma membrane and organelles and/or pyknotic nuclei. Moreover, in ultrastructural morphometry of mitochondrial subcompartments, those mitochondria which showed artifacts due to suboptimal processing were excluded.

The measurements were performed using a Leitz ASM digital image analyzer. The theoretical considerations have been previously discussed by several investigators (Weibel 1969; Smith and Page 1976; Elias and Hyde 1980; Cieciura et al. 1986). The results were compared using the Student's t-test and significant differences were accepted at a level of $P<0.05$.

Sixteen oncocytomas and 11 null cell adenomas were studied in vitro. The 27 tumours were all oncocytomas and null cell adenomas in a series of 95 randomly obtained specimens from pituitary surgical procedures performed at the University of Toronto affiliated hospitals. No patient had clinical or biochemical evidence of adenohypophysial hormone excess. Surgically resected tissues were studied by light microscopy, immunohistochemistry and electron microscopy and were classified on the basis of their morphological features.

Sterile tissue was obtained at the time of surgery. Cells were dispersed and plated as described previously (Asa et al. 1986). Cells were allowed to attach for 2–3 days; subseqeuntly media were collected every 24 h. All media were stored in polyethylene vials at −20° C, until processed for radioimmunoassay (RIA).

Culture medium hormone content was measured by RIA using standard double antibody techniques as described previously (Asa et al. 1986); antisera were directed against GH, PRL, ACTH, TSH, FSH, LH and α-subunit. Intra-assay coefficient of variation (CV) was 5–8% and interassay CV was 7–20%.

Results

The results of light microscopic measurements are shown in Table 1. Compared with null cell adenomas, oncocytomas exhibited significantly greater cell areas and cytoplasmic areas, whereas the nuclear areas were similar. The cytoplasmic areas of oncocytomas were 1.6 times those of null cell adenomas. Consequently, on average, the nuclear/cytoplasmic ratio was 0.34 in oncocytomas

Table 1. Morphometric comparison of oncocytomas and null cell adenomas

Parameter	Oncocytomas mean ± SE	Null cell adenomas mean ± SE
Cellular area (μ^2)	126 ± 12.1*	89 ± 3.1
Nuclear area (μ^2)	32 ± 2.3	32 ± 1.3
Cytoplasmic area (μ^2)	94 ± 9.9*	57 ± 2.2
Cytoplasmic volume density (%)		
Mitochondria	30.8 ± 1.9*	11.8 ± 0.9
Endoplasmic reticulum	4.2 ± 0.3*	6.6 ± 0.5
Golgi apparatus	1.8 ± 0.2	2.2 ± 0.2
Lysosomes	1.0 ± 0.2	0.6 ± 0.1
Secretory granules	3.9 ± 0.4	3.8 ± 0.4
Diameter of secretory granules (nm)	143 ± 5.6	148 ± 4.1
Mitochondrial area ($\times 10^2$ μ^2)	27.4 ± 1.0	25.0 ± 1.0
Surface density of mitochondria (μ^{-1})	2.1 ± 0.1*	0.9 ± 0.1
Surface density per unit mitochondrial volume (μ^{-1})	6.9 ± 0.6	7.5 ± 0.5

* Indicates significant differences from null cell adenomas ($p < 0.05$)
SE: standard error

Table 2. Morphometric characteristic of mitochondria of oncocytomas and null cell adenomas

Compartment and membrane	Parameter	Oncocytomas	Null cell adenomas
Matrix compartment	Volume density (%)	52.4 ± 1.7*	57.8 ± 1.2
Intracristal compartment including cristal membrane	Volume density (%)	30.3 ± 1.6*	24.6 ± 1.0
Inner membrane	Volume density (%)	5.3 ± 0.3*	4.4 ± 0.3
Outer compartment	Volume density (%)	5.8 ± 0.2*	7.9 ± 0.4
Outer membrane	Volume density (%)	5.7 ± 0.2	5.3 ± 0.4
Inner and cristal membrane	Surface density (μ^{-1})	24.6 ± 0.7	23.9 ± 1.2

* Indicates significant differences from null cell adenomas ($p < 0.05$)
All parameters are expressed per unit mitochondrial volume and the mean ± SE

Table 3. Hormone secretion in vitro by null cell adenomas and oncocytomas (expressed as amount/10^4 cells/24 h)

	16 Oncocytomas			11 Null cell adenomas		
	No.	Average	Range	No.	Average	Range
GH (ng)	5	0.3	0.1–0.9	2	1.7	1.5–1.9
PRL (ng)	3	0.3	0.2–0.5	0	–	–
ACTH (Mol)	3	0.7	0.1–1.5	3	2.1	0.5–5.2
TSH (mIU)	2	3.5	3.0–4.0	2	3.0	3.0
FSH (ng)	16	1000	50–5050	11	1550	100–6850
LH (ng)	15	543	21–2153	11	648	105–2362
α-subunit (ng)	16	2.1	0.1–8.1	11	6.6	0.5–18

and 0.56 in null cell adenomas. These results indicate that enlargement of cell areas in oncocytomas is due to an increase in the size of cytoplasm and not that of the nucleus.

The results of ultrastructural measurements are presented in Table 1. The relative cytoplasmic volume density of mitochondria was 30.8% in oncocytomas and 11.8% in null cell adenomas. The difference between the two groups was statistically significant. There was, however, no significant difference in the area of mitochondria and the surface/volume ratio of mitochondria between oncocytomas and null cell adenomas suggesting that the increase of relative cytoplasmic volume density of mitochondria in oncocytomas is caused by increased mitochondrial numbers, and that the size and shape of mitochondria in oncocytomas is not significantly different from that of null cell adenomas. It is noteworthy that relative cytoplasmic volume density of endoplasmic reticulum was smaller in oncocytomas (cytoplasmic volume density of endoplasmic reticulum 4.2%) than in null cell adenomas (6.6%). In contrast, no significant differences were found in the relative cytoplasmic volume density of Golgi apparatus, lysosomes and secretory granules as well as mean diameters of secretory granules of both adenoma types (Fig. 1 and 2).

The results of ultrastructural morphometry of mitochondrial subcompartments are presented in Table 2. In oncocytomas, relative volume density of intracristal compartment, including cristal membrane and relative volume density of inner membrane per unit mitochondrial volume, were significantly greater. Conversely, the relative volume density of matrix compartment and relative volume density of outer compartment per unit mitochondrial volume were significantly lower. In contrast, surface density of inner and cristal membrane per unit mitochondrial volume showed no significant differences between oncocytomas and null cell adenomas.

The amounts of pituitary hormones released into the culture media in 24 h by 2×10^4 cells are summarized in Table 3. The numbers given are the averages of values obtained during one week in vitro. All oncocytomas and null cell adenomas re-

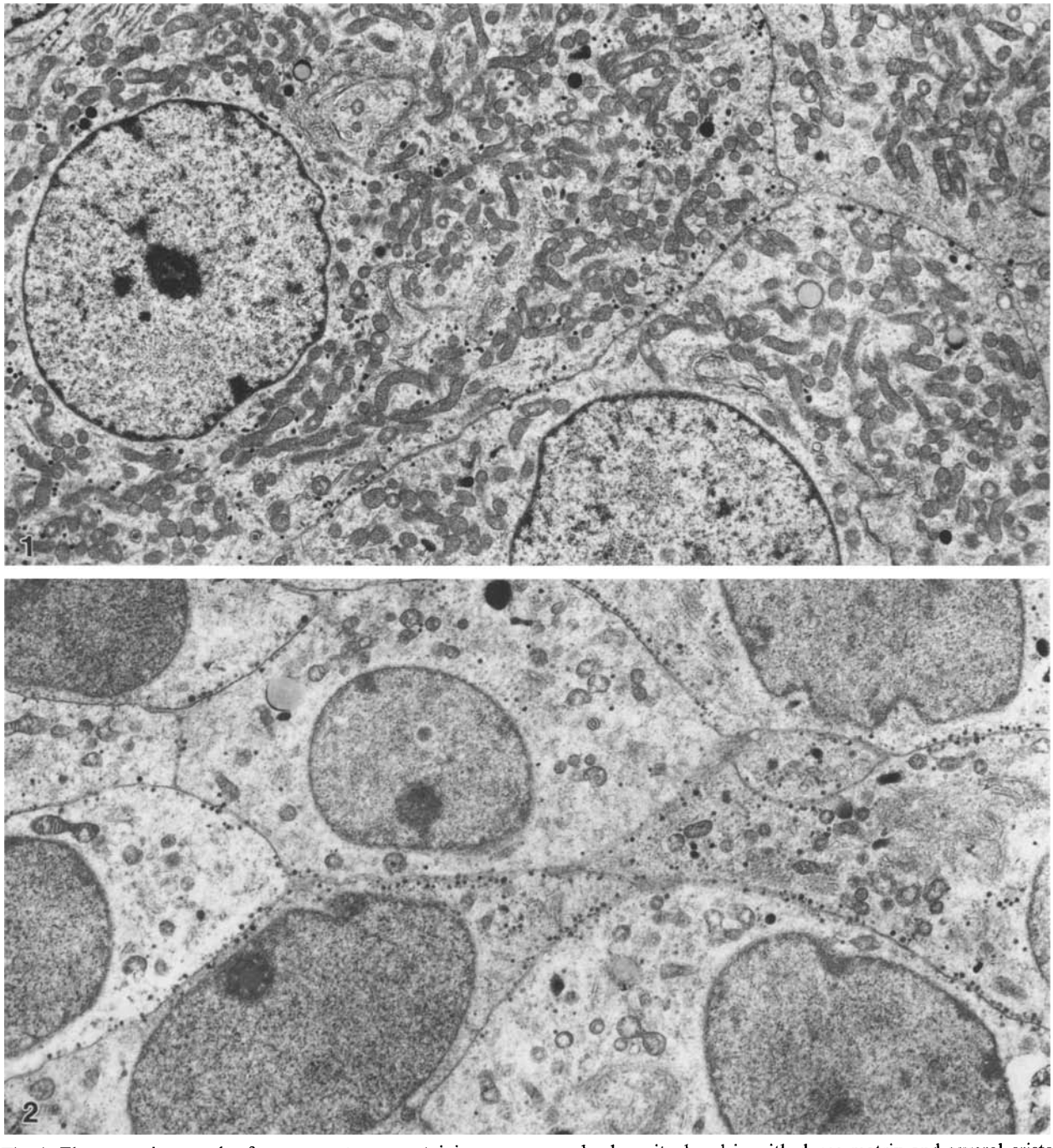

Fig. 1. Electron micrograph of an oncocytoma containing numerous slender mitochondria with dense matrix and several cristae. ×5760

Fig. 2. Electron micrograph of a null cell adenoma composed of polygonal cells with poorly developed cytoplasmic organelles. ×6600

leased significant quantities of glycoprotein hormones, especially gonadotropins and α-subunit. In several instances, small amounts of GH, PRL, ACTH and TSH were detected in culture media, but the values rapidly decreased to undetectable levels. Hormone release by oncocytomas was on average lower than that by null cell adenomas, however, an extensive overlap in the range of hormone release was evident. No hormones were detected in culture medium not incubated with tissue.

Discussion

Recently, Weber et al. (1987) have studied pituitary adenomas using light microscopic morphometry and correlated the degree of oncocytic transformation with clinical and immunohistochemical results. To our knowledge, however, this is the first report of systematic morphometric comparisons between oncocytomas and null cell adenomas and the first study to correlate those data with tissue culture investigations.

Oncocytomas and null cell adenomas are unassociated with clinical or biochemical evidence of hormone excess. Electron microscopy, however, shows features of endocrine differentiation, including the presence of rough-surfaced endoplasmic reticulum, Golgi apparatus and secretory granules (Kovacs and Horvath 1987). Thus, they have all the subcellular organelles necessary for hormone synthesis and release. It may well be that they produce precursor molecules, biologically inactive hormones, hormone fragments, or hormones which have not been identified to date. Alternatively, it is possible that they produce one or more known adenohypophysial hormones at a very low rate.

Consistent with the results of ultrastructural investigation, studies based on immunohistochemistry (Black et al. 1987; Kovacs et al. unpublished work), cell culture techniques (Lipson et al. 1978; Mashiter et al. 1981; Surmont et al. 1983; Asa et al. 1986) and Northern blot methods to determine hormone messenger RNA production (Jameson et al. 1986), have revealed that most of the clinically non-functioning adenomas can produce hormones, primarily glycoprotein hormones.

Our data, which are in agreement with in vitro studies reported so far (Surmont et al. 1983; Asa et al. 1986; Black et al. 1987; Kovacs et al. unpublished work), show that most of these adenomas release glycoprotein hormones, especially FSH, LH and α-subunit. It is noteworthy that the variety and extent of these hormones demonstrated in in vitro studies are the same in oncocytomas as in null cell adenomas.

Morphometric comparison, however, discloses a few differences between oncocytomas and null cell adenomas. Microscopically, the present results, in accordance with other reports (Martinez 1986; Diehl et al. 1987), demonstrate that cell and cytoplasmic areas of oncocytomas are significantly increased; whereas the nuclear areas are similar to those of null cell adenomas.

Some authors (Roy 1978; Kovacs and Horvath 1986; Martinez 1986) have noted that in oncocytomas the ultrastructural appearance and prominence of cytoplasmic organelles, such as endoplasmic reticulum, Golgi apparatus, secretory granules and lysosomes, are similar to those of null cell adenomas, indicating that accumulating mitochondria during oncocytic transformation do not replace other cytoplasmic organelles. In the present study, by visual inspection of the electron micrographs, no significant differences were seen between cytoplasmic organelles other than mitochondria of both adenoma types. Moreover, ultrastructural morphometric results, in agreement with ultrastructural findings, demonstrate that relative cytoplasmic volume density of Golgi apparatus, secretory granules, lysosomes and diameter of secretory granules are not significantly different in oncocytomas from those of null cell adenomas. In contrast to these, the relative cytoplasmic volume density of endoplasmic reticulum is significantly decreased in oncocytomas (4.2%) compared with that of null cell adenomas (6.6%). In this study, the selected magnification was not great enough to differentiate precisely rough endoplasmic reticulum from smooth endoplasmic reticulum. Thus, it remains to be determined whether the decrease of relative volume density of endoplasmic reticulum in oncocytomas is due to reduction of the rough type or smooth type, or both. However, taking into account the enlargement of cell areas (1.4 times in average area) in oncocytomas, it is conceivable that the absolute volume of endoplasmic reticulum per cell might not be reduced compared with those of null cell adenomas and, in the case of the other organelles, migth be even greater than in null cell adenomas. These morphometric data, like the in vitro results, suggest that the functional potential of oncocytomas is not lost.

It has been described that, during oncocytic transformation, mitochondria gradually increase in number and their size, shape and internal structure become abnormal. Mitochondrial gigantism, cavitation of the internal compartment, loss of cristae and their replacement by electron dense, granular material may be apparent (Kovacs and Horvath 1986). In the present study, mitochondria which were swollen and rarefied with lost cristae were avoided because such mitochondria could not be distinguished from artifactually damaged mitochondria and were not suitable for morphometry. The shape and size of mitochondria in oncocytomas are similar to those of null cell adenomas in our material, suggesting that the greater volume density of mitochondria in oncocytomas is due to increased mitochondrial number. Moreover, from the morphometric analysis of mitochondrial sub-

compartments, it becomes apparent that volume density of intracristal compartment and inner membrane including cristal membrane is significantly greater in oncocytomas. However, surface density of inner and cristal membrane per unit mitochondrial volume shows no significant difference between the two adenoma types, indicating that these structures are similar in these adenomas.

The functional significance of mitochondrial abundance in oncocytomas has been discussed using histochemical (Balogh and Roth 1965; Bedetti 1985) and biochemical data (Tandler et al. 1970). It has been suggested that oncocytic change represents the morphological expression of an obscure mitochondrial disease (Tremblay 1969). The present data may suggest the possibility that mitochondrial abundance and enlargement of volume density of intracristal compartment including cristal membrane and inner membrane reflect an effort of the cell to compensate for an unknown biochemical defect at the organelle level.

There is still controversy concerning whether oncocytic transformation precedes or follows tumour formation (Kovacs et al. 1974) and it is obscure as to what kind of tumours may preexist – null cell adenomas, functioning adenomas, or both. Further studies, including ultrastructural morphometric comparison of adenomas in the various stages of oncocytic transformation, are required to solve the cytogenesis of oncocytomas.

In summary, it can be concluded that oncocytomas, which represent the final stages of oncocytic transformation, have a close relationship with null cell adenomas based on morphometric comparison as well as in vitro studies.

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