Salivary Gland Monomorphic Adenoma

Ultrastructural, Immunoperoxidase, and Histogenetic Aspects

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Monomorphic adenoma of basal cell type is a salivary gland tumor believed to result from a proliferation of a single type of cell. However, ultrastructural and immunocytochemical investigations of 6 monomorphic adenomas (5 from parotid and 1 from intraoral minor salivary gland) indicate that there are two classes of these lesions, one composed of two types of tumor cells and the other wholly or predominantly made up of one type of cell (isomorphic). In the former group, the organization of the tumor cells closely mimicked that of normal and hyperplastic salivary gland intercalated ducts. Aggregates of tumor cells were arranged as an inner layer of luminal epithelial cells which were surrounded by an outer layer of cells that, in some cases, had ultrastructural and immunohistochemical features indicating myoepithelial cell differentiation. In some adenomas formed by two types of tumor cells, basal-lamina-lined extracellular spaces were identified ultrastructurally in relation to modified myoepithelial cells; such spaces had the same fine-structural features as those reported in pleomorphic adenoma and adenoid cystic carcinoma. Predominantly isomorphic adenomas were composed exclusively of luminal epithelial cells. These results indicate that despite the varied histologic patterns in the numerous subtypes of monomorphic adenoma, there is a central theme of differentiation and organization in this type of neoplasm which recapitulates the ductoacinar unit of normal salivary gland parenchyma. (Am J Pathol 1984, 115:334–348)

A NUMBER of principles have been used in attempts to classify salivary gland tumors. Systems based on histogenesis use the type of cell predicted as the specific precursor cell that has undergone neoplastic transformation. In the case of monomorphic adenoma of basal cell type, many cell types have been implicated. These include the intercalated or striated duct cell,[1,2] the intercalated duct reserve cell,[3–5] the intralobular duct cell,[6] the interlobular duct cell,[7] and the serous acinar cell.[8] Such suggestions have been based largely on fine-structural similarities between the various cellular components of normal ducts and acini and basal cell adenoma tumor cells.

Most current classifications of salivary gland monomorphic adenomas use a variety of principles, including type of cell, cellular arrangement, and embryologic development, and, as a result, could represent a heterogeneous group of tumors in terms of histogenesis. In addition, the relationship of the various monomorphic adenomas to other salivary gland tumors remains unclear. Many basal cell adenomas are assumed to be composed of a single type of tumor cell, because of the monotonous cytologic features of these tumors in routine histologic preparations. The majority of previous ultrastructural studies have tended to support this impression and, in particular, have usually failed to indicate the presence of myoepithelial cells in this lesion.[6–12] However, some forms of these tumors may be bimorphic, and myoepithelial cells may account for one of the cell types.[2,5,13–16] In terms of histogenesis, basal cell adenomas are presumed to arise as a result of neoplastic induction of a hypothetical intercalated duct reserve cell and are thought to represent one aspect of the potential bidirectional differentiation—ducts and acini—of this stem cell.[3]

The present study presents the ultrastructural and

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Table 1 –

	Clinical data		Immunoperoxidase results			
	Age/Sex	Size (cm)	Cell layer	EMA	CK	S-100 protein
Two-cell type						
Case 1	60/M	1.5 × 1.0	Central	+	+	–
			Basal	–	–	–
Case 2	31/F	1.0 × 1.0	Central	+	+	–
			Basal	–	–	+
Case 3	55/F	3.0 × 2.5	Central	+	+	–
			Basal	–	+	+
Case 4	46/F	1.0 × 1.0	Central	+	+	–
			Basal	–	–	–
One-cell type						
Case 5	54/F	2.0 × 1.8		+	–	–
Case 6	42/F	2.5 × 2.0		+	+	+

immunohistochemical findings in a group of 6 monomorphic adenomas of major and minor salivary gland origin in comparison with fine-structural features of the intercalated duct of parotid salivary gland.

Materials and Methods

Microscopy

Case material for light- and electron-microscopic study of salivary gland tumors was obtained from the surgical pathology files of the Toronto General Hospital, Toronto, Canada, and the Canadian Tumour Reference Centre, Ottawa, Canada. Formalin-fixed paraffin-embedded tissues were available for routine microscopic review. Alcian blue (pH 1.0 and 2.5)/periodic acid–Schiff (PAS) staining, with and without bovine testicular hyaluronidase (Sigma Chemical Co.) digestion, was done on paraffin sections in selected cases.

For electron microscopy, material fixed with Karnovsky's solution was available in 5 of the cases, and tissue fixed with buffered formalin (10%), in 1 case. These tissue samples had been postfixed in osmium tetroxide, dehydrated in graded alcohols, and embedded in Epon-araldite. Toluidine-blue–stained, 1-μ thick plastic sections were used for selection of appropriate areas for ultrastructural examination. Thin sections were stained with uranyl acetate and lead citrate and examined in a Philips EM 200 or 301 electron microscope.

Immunostaining

Immunoperoxidase staining was performed on formalin-fixed, paraffin-embedded tissue sections with the use of rabbit antibodies to epithelial membrane antigen (EMA), Mallory body cytokeratin (CK) and S-100 protein, and a peroxidase anti-peroxidase technique.

The goat anti-EMA (Sera-Lab, Sussex, England) reacted with the luminal surface of normal ductal and glandular epithelial cells.[17] Mallory bodies were isolated from alcoholic human liver obtained at autopsy, and an anti-CK antiserum was produced in rabbits.[18] This reacted with various epithelial cells, including normal salivary ducts and myoepithelial cells. The S-100 protein was purified from beef brain, and an antiserum was obtained by immunizing rabbits.[19] As positive controls, sections of normal breast tissue (anti-EMA), liver (anti-CK), and brain (anti-S-100 protein) were stained with these antibodies. As a negative control, normal rabbit serum was used instead of the antibodies.

Results

Light Microscopy and Immunoperoxidase Staining

Clinicopathologic data of the 6 cases is provided in Table 1. All tumors were small, well-encapsulated nodules and, with the exception of Case 5 (oral mucosa of the cheek), were located in parotid salivary gland.

As is evident from Figures 1–6, these tumors were highly cellular, with the range of histologic patterns (solid, tubular, and trabecular) characteristic of basal cell adenomas. In most cases, sections of paraffin-embedded tissue produced the impression of an isomorphic population of tumour cells (Figures 3–6); but at higher magnification in Case 1 (Figure 1), there was a suggestion that the tubulotrabecular cords were formed by a two-tiered epithelium. In the plastic-embedded tissue of Case 2 (Figure 2), anastomosing columns of tumor cells were clearly formed by a larger, paler-staining central element that was bordered on either side by palisaded smaller darker-

staining tumor cells. Four of the 6 tumors showed the formation of glandular lumens (Figures 1, 3, 5, and 6), while cases 2 and 4 revealed the presence of numerous, irregularly shaped, and frequently anastomosing "stromal" regions with a homogeneous or reticulated appearance (Figures 2 and 4).

The results of immunostaining (Table 1) revealed that all cases contained a tumor cell component that stained for EMA. Staining was either confined to apical regions or was diffusely distributed throughout the cytoplasm, regardless of whether or not lumen formation was present. In the first 4 cases, EMA-positive tumor cells were located central to an outer layer of non-EMA–staining cells. In all of these cases, centrally oriented cells were also positive with antibody to CK (Figure 7), but only in Case 3 did the outer layer of tumor cells also stain for this CK (Table 1). Three of the 6 tumors stained focally or diffusely with antibody to S-100 protein. In Case 2, diffuse cytoplasmic and nuclear staining was confined to the outer palisaded layer of tumor cells, while in Case 3, anti-S-100 protein staining was present in extensive regions of polygonal and spindle-shaped cells (Figure 8), among which were scattered a few islands of cells that only stained with antibody to EMA and CK. Anti-S-100 protein staining in Case 6 was noted in scattered small clusters that appeared to bear no relationship to the predominant tumor cells staining with antibody to EMA and CK that were often associated with secretory lumens (Figure 6).

Ultrastructural Observations

Intercalated Duct of Normal Salivary Gland

The morphologic and cytologic features of hyperplastic intercalated ducts observed in the partially atrophic salivary gland tissue which was resected with a parotid carcinoma ex pleomorphic adenoma served as a model for assessing ultrastructural features of basal cell adenomas. All intercalated ducts had an inner layer of cuboidal luminal epithelial cells surrounded by the narrow, more darkly staining, cytoplasmic processes of myoepithelial cells (Figure 9). These processes, containing microfilaments and linear densities, were more obvious than in normal ducts and completely, or nearly completely, encompassed luminal cells (Figure 9). Occasionally, the triangular-shaped cell body of a myoepithelial cell was wedged between luminal cells (Figure 9, inset).

Adenomas of Two-Cell Type

Electron micrographs from the case illustrated in Figure 1 (Case 1) provided the best example of the differentiation of two types of tumor cells in basal cell adenoma. Glandular structures were formed by central, well-aligned, and closely associated epithelial cells (with apically situated secretory granules), encompassed by a continuous layer of smaller, more densely staining tumor cells (Figure 10). The latter cells, in addition to having more irregularly shaped nuclei, occasionally contained secretory-type granules, tonofilament bundles, microfilaments with linear densities, and hemidesmosomes associated with the basal lamina (Figure 10).

Cases 2 and 3, illustrated in Figures 2 and 3, respectively, although differing somewhat in their architectural organization, had similar features ultrastructurally. Figure 11 is a representative area from Case 3. Lumen-associated cells were relatively large and pale-staining and had irregularly shaped or deeply indented nuclei with markedly disaggregated chromatin. Peripheral to these cells, a row of smaller, more darkly staining, and more irregularly shaped cells with a high nuclear/cytoplasmic ratio were evident (Figure 11). The majority of the cells had few cytoplasmic specializations. However, focal groups of tumor cells in the basal layer contained prominent amounts of parallel microfilaments within which were elongated and densely staining structures (Figure 12). The zone between nests of tumor cells consisted of an intricate network of basal lamina (Figure 11), and focal accumulations of a similar material were also evident within the cellular aggregates (Figure 11, inset). Tumor cells with cytologic features transitional between those of lumen-associated and basal-oriented cells were occasionally noted, and a few basal cells were involved in lumen formation (Figure 11). By light microscopy, in the basal cell adenoma of Case 2, there was an apparent lack of ductal or glandular formation (Figure 2). However, well-defined glandular lumens were readily apparent ultrastructurally, and luminal epithelial cells contained tonofilament bundles (not illustrated).

In histologic sections, the fourth adenoma in this group had a solid to trabecular pattern formed by polygonal and plump spindle-shaped cells (Figure 4). Initial review of electron micrographs suggested a single cell population, but a more critical appraisal revealed infrequent groups of elongated, slightly paler-staining tumor cells within the more numerous, more darkly staining spindle cell component (Figure 13). The paler cells formed small but distinct glandular-type lumens with typical zonulae occludentes and short blunt microvilli (Figure 13). Among the more darkly staining cells that formed major portions of this adenoma, small basal lamina-lined extracellular spaces were evident (Figure 13). Such microcystic

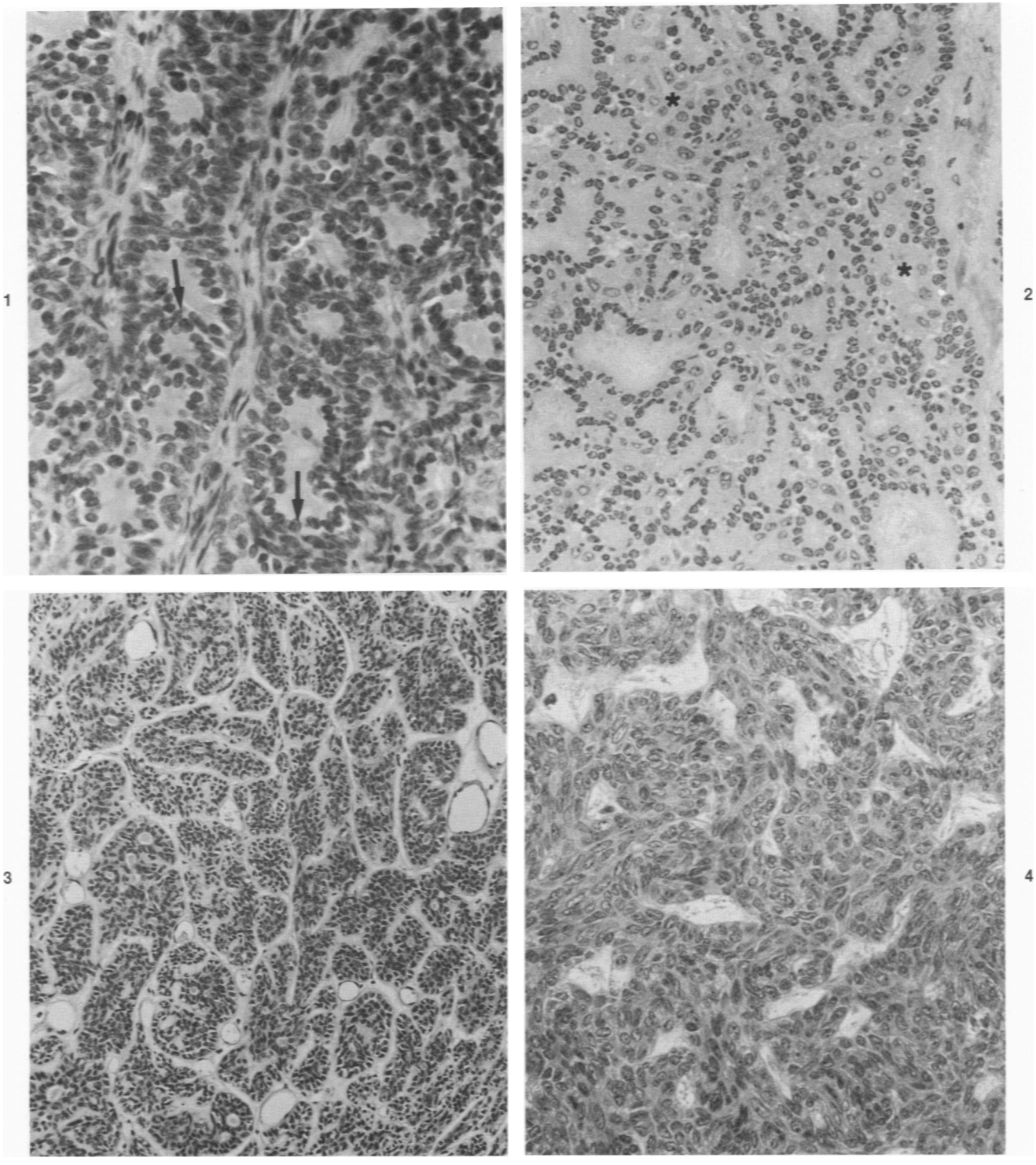
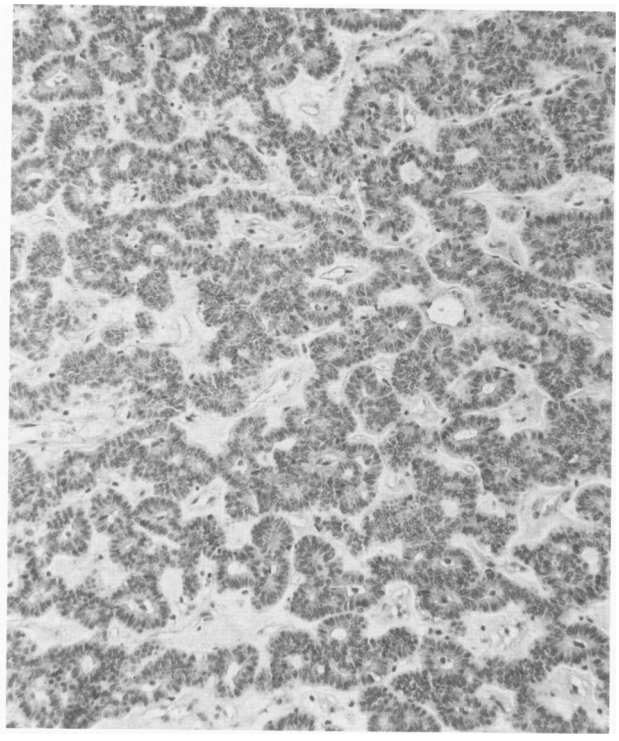
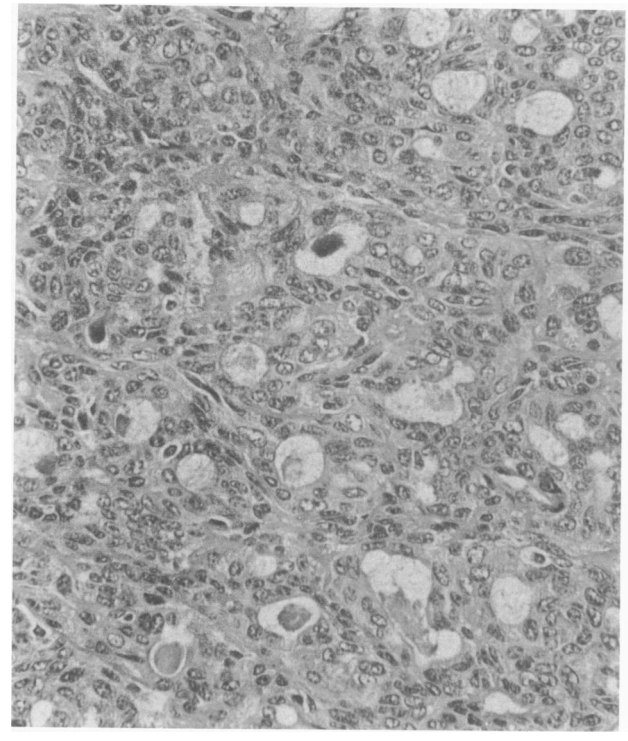
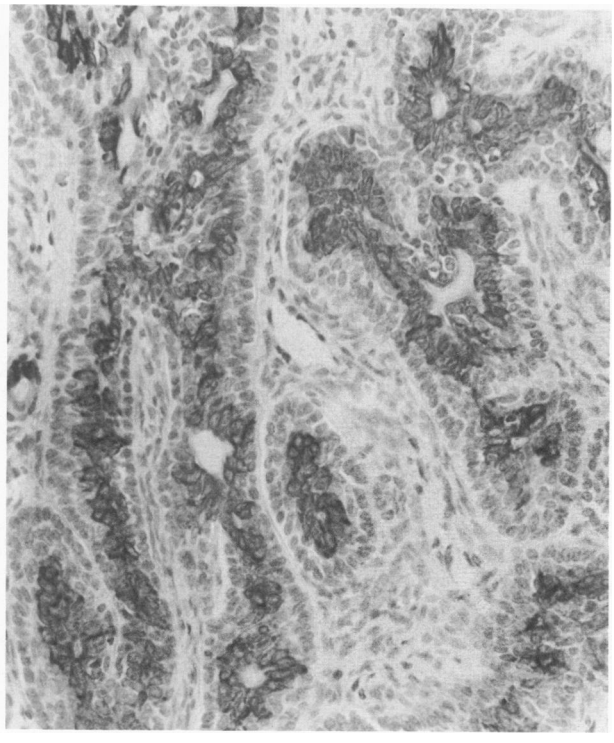


Figure 1 – Case 1. Basal cell adenoma composed of sheets and closely associated cords of uniform tumor cells forming numerous lumens. Some areas suggest two-cell layering with a slightly darker staining cell layer associated with the lumen (*arrows*). (H&E, × 350) **Figure 2** – Case 2. Intricately anastomosing cords of tumor cells are composed of an outer layer of small cells enclosing a larger, paler staining component (*asterisks*). (Toluidine blue (epon section), × 350) **Figure 3** – Case 3. Basal cell adenoma partially formed of sharply outlined clusters composed of angulated tumor cells enclosing small lumens. Other areas were formed of sheets of spindle cells. (H&E, × 130) **Figure 4** – Case 4. A solid type of basal cell adenoma composed of polygonal and plump spindle-shaped tumor cells among which are irregularly shaped and sized stromal regions. (H&E, × 350) (All with a photographic reduction of 4%)







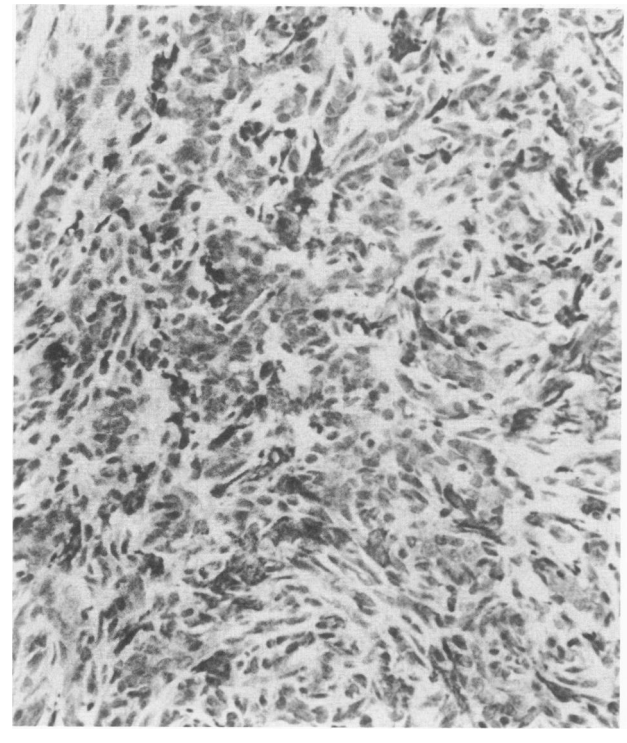


Figure 5—Case 5. Uniform low columnar cells form a number of lumens in this example of basal cell adenoma with a tubular or canalicular growth pattern. (H&E, ×130) **Figure 6**—Case 6. Glandular lumens are scattered within the polygonal cell population of this largely solid type of salivary gland adenoma. (H&E, ×350) **Figure 7**—In a region from Case 1 (Figure 1) with a more trabecular pattern, antibody to CK intensely stains central cells in relation to lumens, while basal cells are unstained. Anti-EMA antibody produced a similar pattern of staining. (Immunoperoxidase, hematoxylin counterstain, ×350) **Figure 8**—The spindle cell region of Case 3 has a proportion of the spindle cells staining positively with antibody to S-100 protein. (Immunoperoxidase, hematoxylin counterstain, ×300) (All with a photographic reduction of 4%)

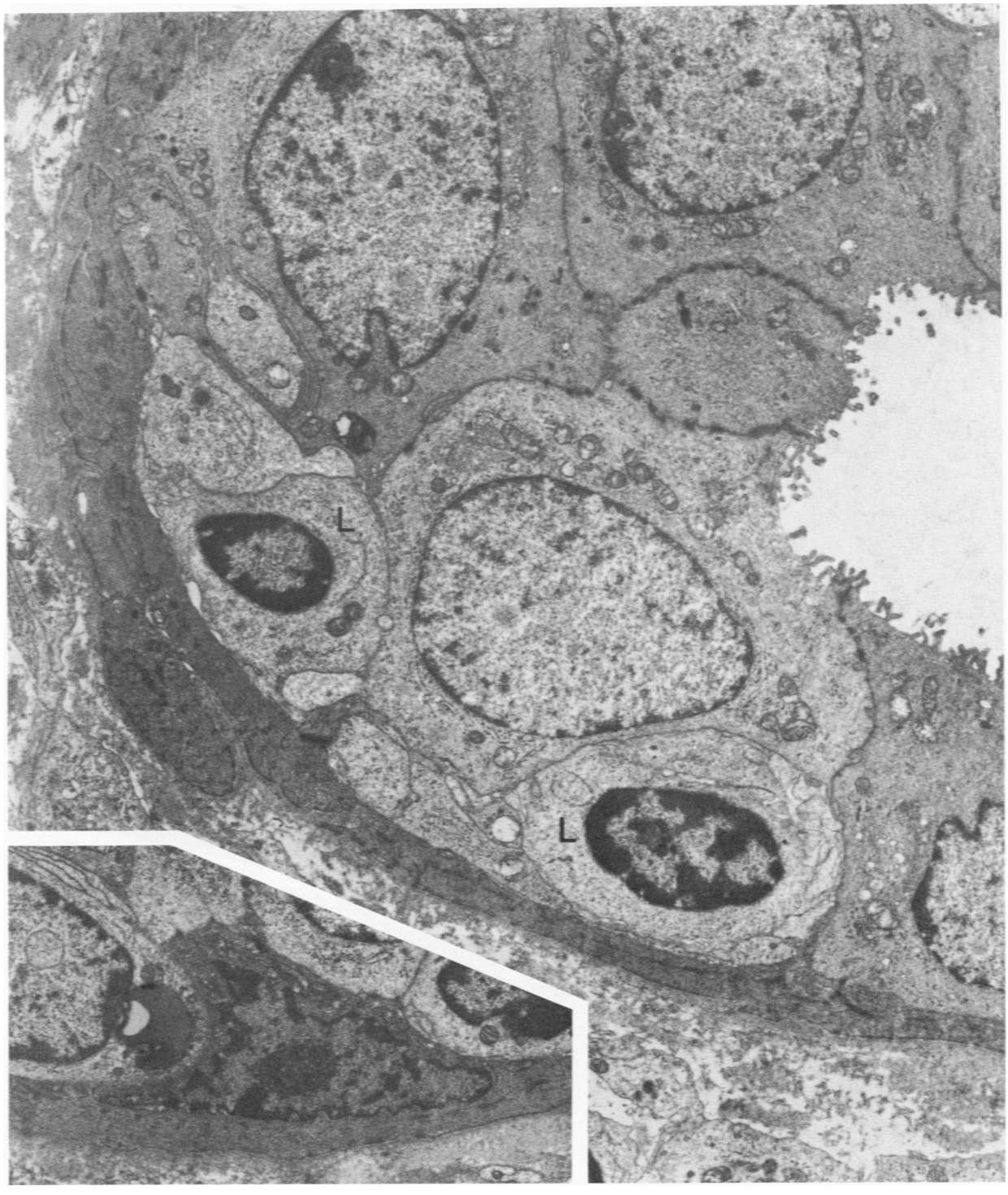


Figure 9 – Hyperplastic intercalated duct in atrophic parotid salivary gland has cuboidal luminal epithelial cells surrounded by elongated, more electron-dense cytoplasmic processes, and the occasional cell body (**inset**), of myoepithelial cells. Lymphocytes (*L*) infiltrate the duct. (×7800; **inset**, ×7200) (With a photographic reduction of 5%)

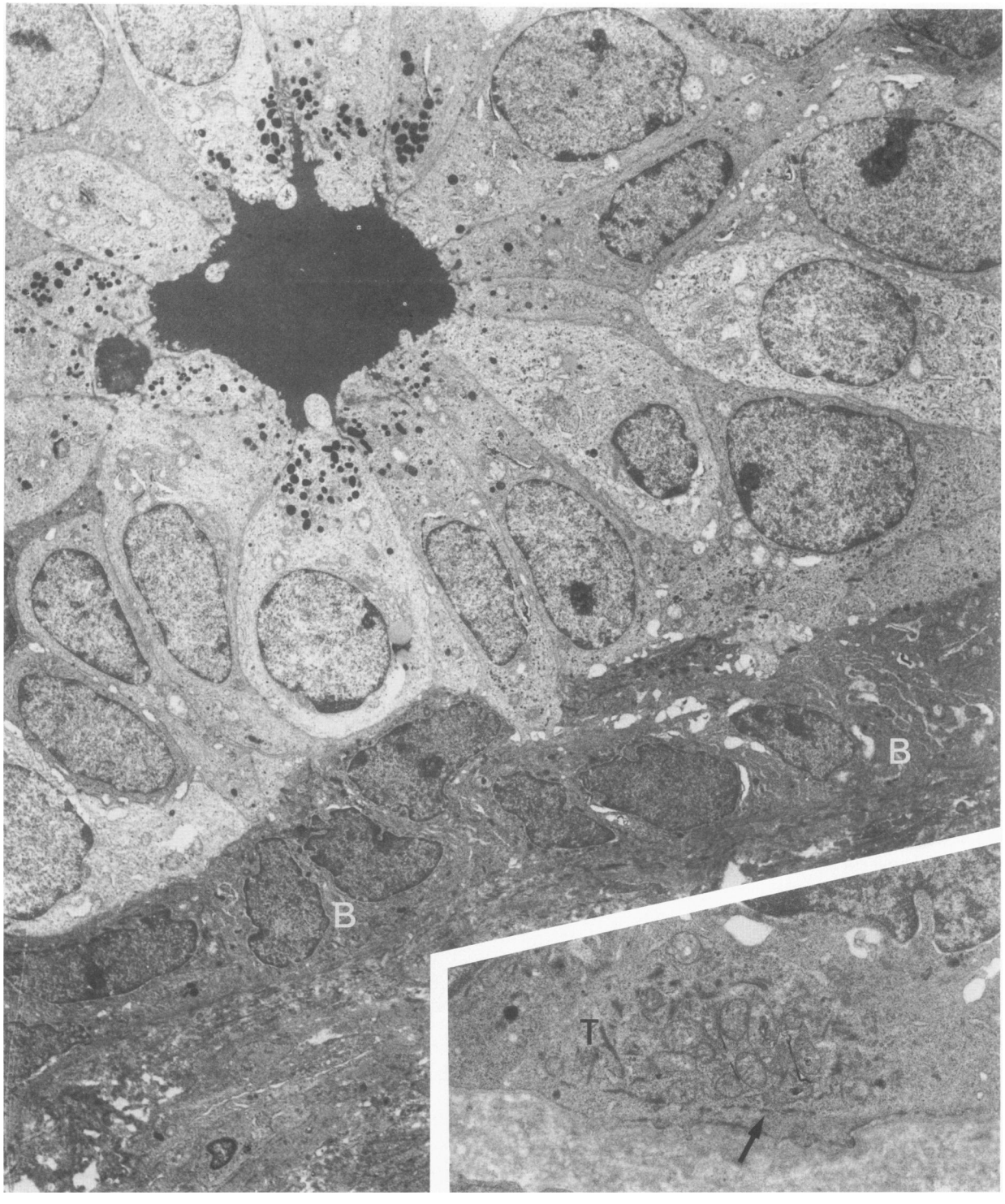


Figure 10—Case 1. Electron micrographs confirm the formation of glanduloductal lumens by electronlucent luminal cells containing apical secretory granules. A distinct basal layer (*B*) is formed by smaller, electron-dense tumor cells that have a few dense granules, microfilaments with dense bodies (*arrow*), hemidesmosomes, and, occasionally, tonofilaments (*T*) (**inset**). (× 4300; **inset**, × 10,500) (With a photographic reduction of 4%)

spaces, with reduplicated basal lamina and granulofibrillar materials, appeared to enlarge and coalesce (Figure 14), so that they were apparent in routine sections (Figure 4).

Adenomas of One-Cell Type

In Cases 5 and 6, despite considerable differences in histologic growth patterns between the two tumors in this category (Figures 5 and 6), both tumors were very similar ultrastructurally. Figure 15, a section from the basal cell adenoma of minor salivary gland origin (Case 5 and Figure 5), was representative of both lesions. The principal feature was the columnar epithelial cells extending from the lumen to the outer aspects of the cell clusters without evidence of a second type of cell at the periphery (Figure 15). Nuclear and cytoplasmic features of these cells were similar to those of luminal epithelial cells in hyperplastic intercalated ducts (Figure 9) and in the tumors with a dual cell population described in the preceding section (Figures 10, 11, and 13).

Discussion

There have been divergent interpretations of the cellular organization of salivary gland monomorphic adenomas. Some reports have stressed an isomorphic tumor cell population,[5,8,9-11,20-23] and other studies have suggested a bimorphic pattern of differentiation.[2,14-16,24] The classification proposed by Thackray and Lucas[13] recognized that salivary gland adenomas could be composed of one or two types of tumor cells. What has been more difficult to verify is the role of the myoepithelial cell in monomorphic adenomas. Thackray and Lucas[13] and Batsakis et al[24] have concluded that myoepithelial cells cannot be excluded from a role in this tumor class. An additional question is the relationship of monomorphic adenoma to pleomorphic adenoma.

The present report indicates that, on histologic grounds, basal cell adenomas subdivide into two categories, one with bidirectional differentiation and the other entirely or predominantly formed by a single type of cell. Others have recognized the heterogeneity of tumor cell populations in some basal cell adenomas,[13-16,24,25] but it is apparent that it may be difficult to do so in routine histologic sections. However, as indicated by our immunoperoxidase results and survey-type electron micrographs, two types of tumor cells were revealed in basal cell adenomas. In addition, the organization of the two types of tumor cells appears to reflect that of the intercalated duct and acinus of normal salivary gland. With these morphologic features and the uniform therapeutic and prognostic aspects of basal cell adenomas, it would seem reasonable to follow the suggestion of Nagao et al,[25] and subdivide basal cell adenoma on the basis of predominant cell type or histologic pattern (basal cell or solid type, tubular type, trabecular type, clear cell type, myoepithelioma, etc.) regardless of whether one or two types of tumor cell are actually involved.

A number of studies have shown staining of luminal-type epithelial cells in normal salivary gland and in benign and malignant salivary gland tumors using antisera in EMA and CK.[26-29] In the basal cell adenomas in the current series, antibodies to EMA and CK clearly define neoplastic epithelial cells aligned in relation to potential or developed lumens, with or without a peripherally oriented tumor cell. This latter cell component may or may not stain with antiserum to CK protein, possibly reflecting the variability of genetic expression or the presence of phenotypically specific subtypes of this and other proteins in these tumors. Prekeratin filaments have been identified in normal myoepithelial cells of salivary gland[26-28,30]; so it is not unexpected that tumor cells in the outer layer in Case 3 would stain positively for these proteins.

The specificity of antibodies to intracellular proteins in various cell types is illustrated by the staining patterns of antibodies to epidermal and hepatic cytokeratins in normal human and rat mammary tissue and in intraductal carcinomas of human breast.[31] In addition, antibodies to human epidermal CK raised in two different animals produce different patterns of staining in mouse mammary tissue.[32] We have also noted complementary staining of myoepithelial and luminal cells in normal rat salivary gland, using antisera to epidermal and Mallory body CK, and significant alterations in the expression of CK intermediate filaments during the development of squamous metaplasia in rat salivary gland.[33] Heterogeneity in the detection of these various immunologic markers in the present cases of basal cell adenoma is to be expected,[34] and it would seem to reflect the variability in differentiation of myoepitheliumlike cells noted in the ultrastructural observations. The fact that peripherally oriented tumor cells infrequently stained positively with Mallory body CK antibody indicates that either these cells produced intermediate filaments other than CK or the Mallory body CK antibody does not cross-react with the CK filaments of these cells. The latter seems most likely, because the cytokeratins are known to be a heterogeneous group of polypeptides, with the composition of cytokeratins differing in different epithelial tissues.[35,36] Expression of CK polypeptides are also altered in epithelial neoplasms.[35] It

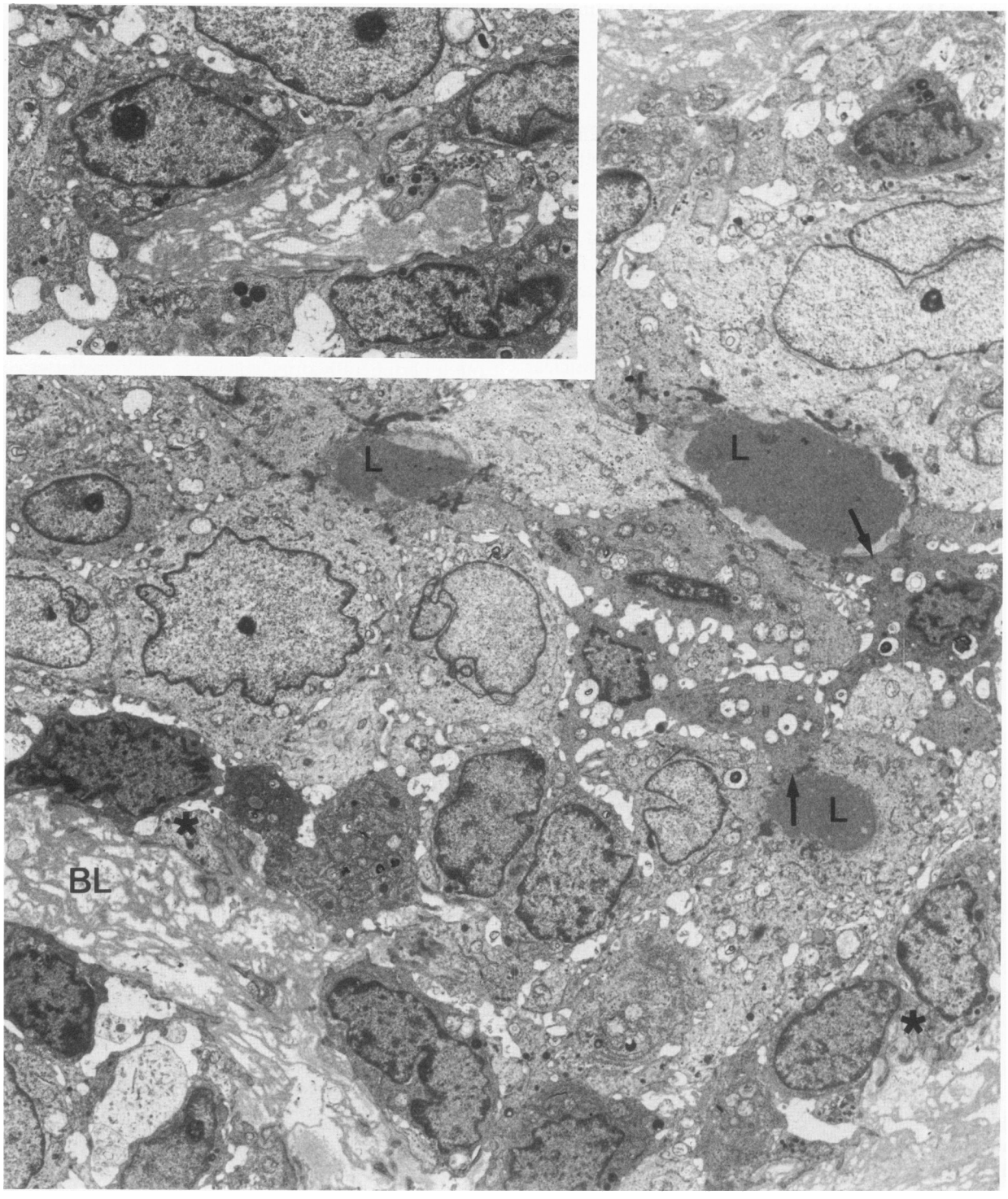


Figure 11 – Case 3. Cell clusters, separated by reduplicated basal lamina (*BL*), were composed of larger, paler-staining tumor cells associated with lumens (*L*) and smaller, more electron-dense cells forming a peripheral basal layer (*asterisks*). Basal cells were sometimes involved in lumen formation (*arrows*). Formation of discrete basal lamina-containing intercellular spaces was observed well within tumor cell clusters (**inset**). (×4300; **inset**, ×5000) (With a photographic reduction of 4%)

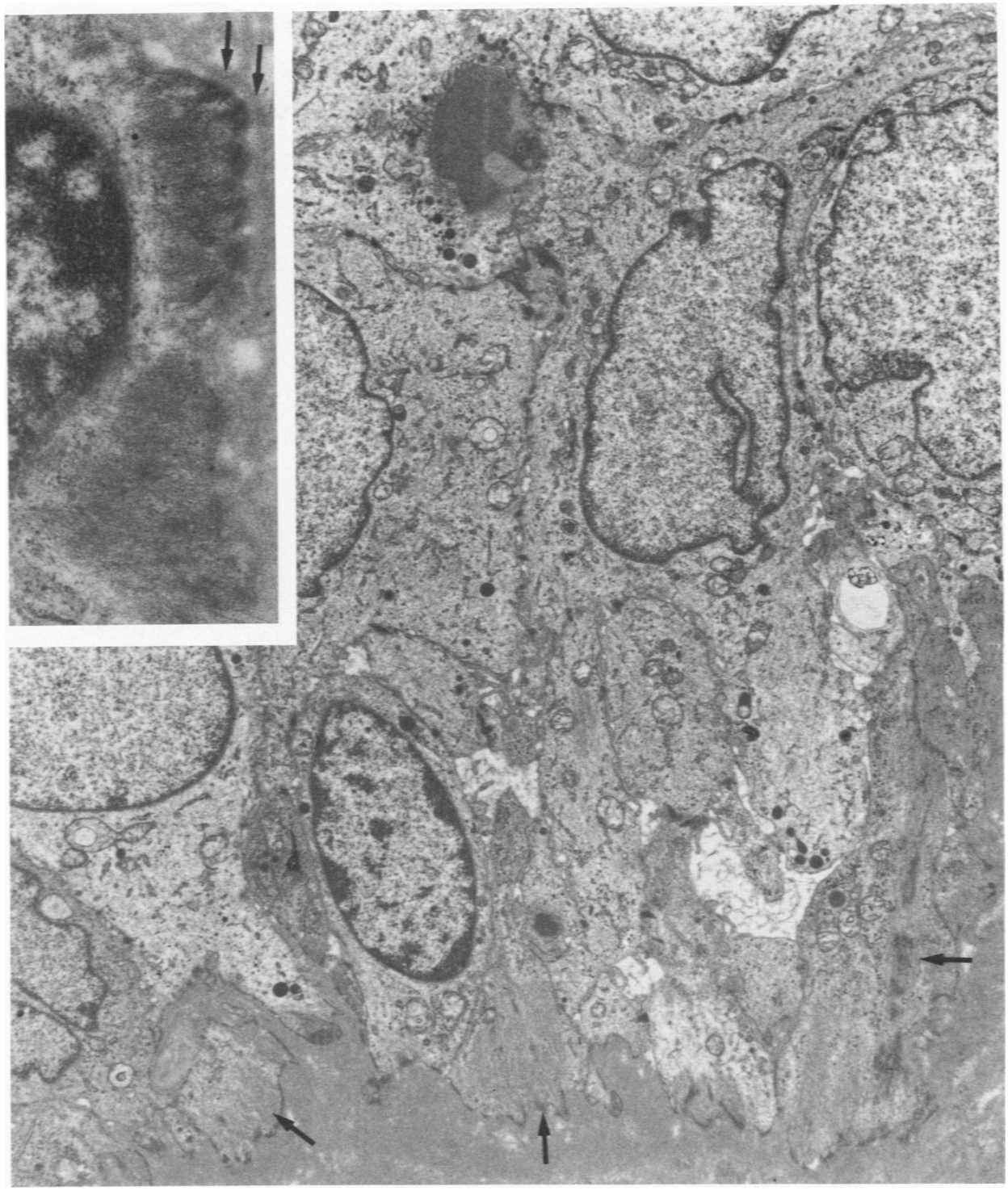


Figure 12 – Case 3. Portions of the cytoplasm of basal cells contain focal accumulations of filaments (*arrows*) associated with elongated densities and plasmalemmal plaques. Hemidesmosomes (*arrows*) are associated with subplasmalemmal densities and basal lamina (**inset**). (×7800; **inset**, ×33,600) (With a photographic reduction of 4%)

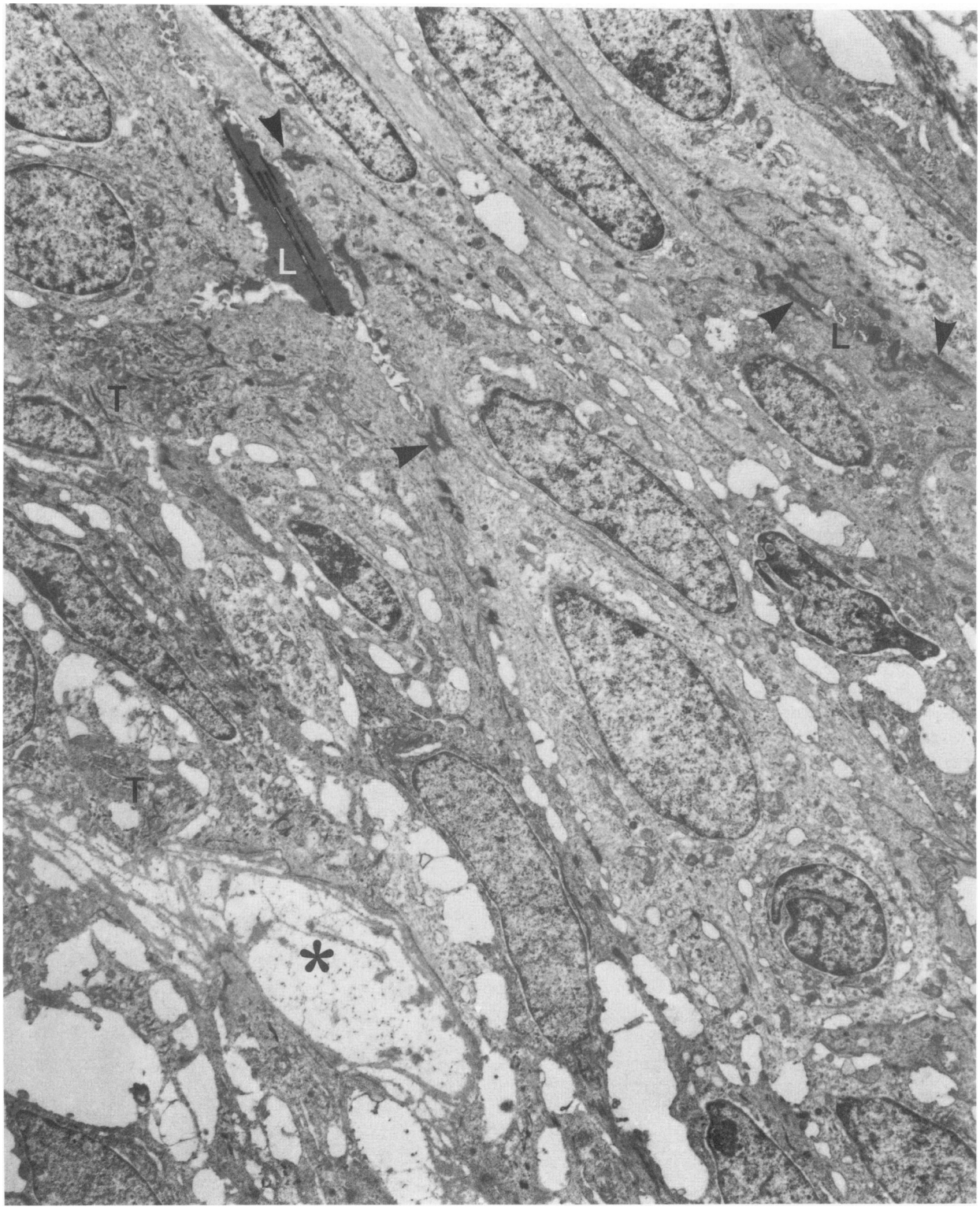


Figure 13 – Case 4. Groups of paler-staining tumor cells with small intercellular lumens (*L*), short microvilli, and zonulae occludentes (*arrowheads*) are surrounded by a more numerous, slightly more darkly staining spindle-cell population with tonofilaments (*T*). The latter cells enclosed basal-lamina-lined microcystic intercellular spaces (*asterisk*). (×4000)

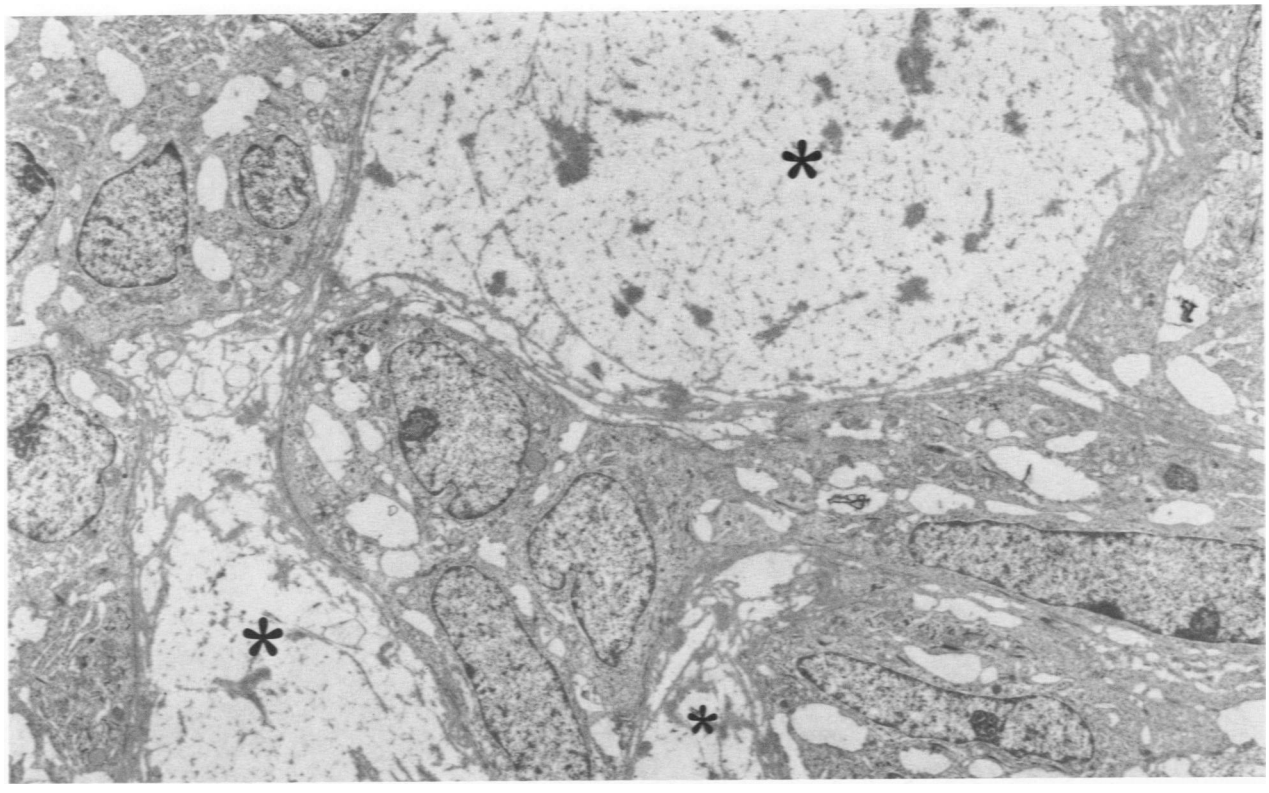


Figure 14 – Case 4. Between the spindled and irregularly shaped tumor cells are intercellular spaces of various sizes (*asterisks*) containing reduplicated basal lamina and granulofibrillar proteoglycans. Some intercellular spares appear to merge. (× 3800) (With a photographic reduction of 5%)

would, therefore, not be unexpected that the CK composition is altered as myoepithelial cells become structurally modified in basal cell adenomas.

In those examples of basal cell adenoma staining with antibody to S-100 protein (Cases 2 and 3), luminally arranged tumor cells remained unstained, and the distribution of stained cells in a peripheral location suggested that the latter could be of myoepithelial differentiation. S-100 protein has been identified in myoepithelial cells of normal breast and salivary gland in association with ducts and acini.[37] As in basal cell adenomas, the distribution of S-100-protein-positive tumor cells in pleomorphic adenoma has also suggested the myoepithelial nature of this component.[37,38] Interpreting histochemical findings in a case of basal cell adenoma, Harrison[14] indicated the presence of myoepithelial cells in this tumor; and Jao et al,[1] on the basis of ultrastructural findings, suggested that there might be transitional forms of myoepithelial cells in salivary gland tumors.

From the results of the present 6 cases, it is apparent that in basal cell adenomas, it is the arrangement and proportion of the two types of tumor cells which are responsible for the variety of subtypes, and also the variations in histologic patterns in individual tumors. Case 3 illustrates this. In Figure 3, the arrangement is of discrete nests with well-defined ductlike lumens surrounded by angular tumor cells. However, in the region of this tumor illustrated in Figure 8, the tumor cells are almost entirely S-100-protein-positive myoepithelial cells with only a few scattered EMA-positive lumens; a lesion with this predominant pattern would be labeled a myoepithelioma. An adenoma with this type of differentiation has been reported by Chaudhry et al.[12] Similarly, although the immunohistochemical and ultrastructural findings indicated an almost exclusively isomorphic population of tumor cells of luminal epithelial type in Case 6, a few small scattered regions of S-100-protein-positive tumor cells were apparent, suggesting that even this tumor had a minor population of myoepithelial cells.

Most previous ultrastructural reports of basal cell adenoma have stated that myoepithelial cells are absent as a component of these neoplasmas.[8-11,23] Tumor cells on the periphery of cell nests and columns in basal cell adenoma infrequently express the characteristic fine-structural features of fully differentiated myoepithelial cells. However, as observed in Figures 10 and 12 (Cases 1 and 3) and reported by Suzuki,[2] a significant number of tumor cells with

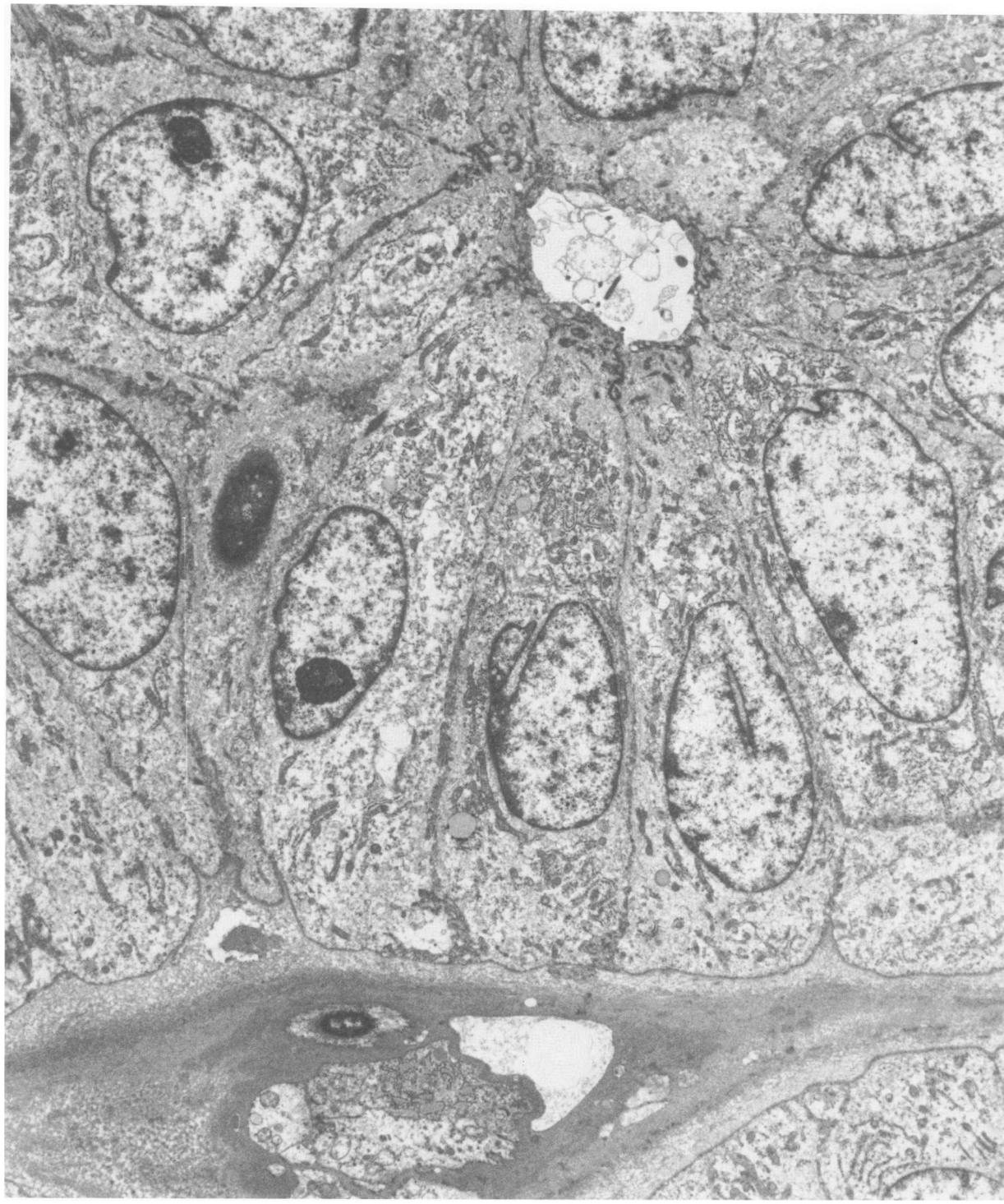


Figure 15—Case 5. Columnar, lumen-forming tumor cells extend to the basal-lamina-forming outer aspects of the cell clusters. No second cell component was interposed between these cells and the capillary-containing stroma. (×5600) (With a photographic reduction of 5%)

some degree of myoepithelial cell differentiation do occur in a number of basal cell adenomas. Irrespective of the degree of differentiation, there is a tumor cell component aligned in relation to luminal-type cells in a pattern mimicking the composition of normal and hyperplastic intercalated ducts. Thus, the palisaded cells on the outer aspect of cell nests in basal cell adenomas, even without typical features of myoepithelium, are suggested to represent neoplastically modified myoepithelial cells. A similar organi-

zation and modification of myoepithelial cells is also evident in pleomorphic adenoma,[39-41] adenoid cystic carcinoma,[42-46] and mucoepidermoid carcinoma.[47] A spectrum of myoepithelial cell differentiation is apparent in ultrastructural reports of myoepitheliomas of salivary gland origin.[12,48]

An additional important structural feature of basal cell adenoma is the presence of sharply defined extracellular spaces noted in both light- (Cases 2 and 4, Figures 2 and 4), and electron-microscopic studies (Case 3, Figure 11, and Case 4, Figures 13 and 14). It is apparent from the ultrastructural findings that these tissue spaces are lined by external lamina and contain replicated lamina and amorphous and granulofibrillar materials that stain histochemically for acidic mucosubstances.[14] Others have observed this extracellular compartment in basal cell adenoma in electron micrographs,[1,6,25] but its significance has not been fully appreciated. As observed in this report, the replicated external lamina, whether occurring in regions between cellular nests or columns or within the aggregates of tumor cells, was noted to develop primarily in relation to modified myoepithelial cells. A similar process occurs in pleomorphic adenoma.[40,41] Furthermore, the pseudocystic spaces of adenoid cystic carcinoma share the same fine-structural and developmental processes evident in basal cell adenomas and pleomorphic adenomas.[42-46] Such information has important connotations for the histogenetic relationship of these three types of salivary gland tumors.

Accumulating ultrastructural and immunohistochemical observations suggest that despite a wide histomorphologic variation in basal cell adenomas, there is a common pattern of differentiation and cellular organization in these tumors. This pattern involves recapitulation of ductal or acinar differentiation, with or without the presence of myoepithelial cells, although in many cases such an organization cannot be readily appreciated in routine histologic sections. Further histologic diversity in basal cell adenomas is produced by the degree of formation of discrete extracellular spaces, the production of basal lamina and other secretory products, and the balance between proliferation of luminal epithelial cells of ductal or acinar type and myoepithelial cells. Even such an entity as membranous adenoma[15,24] is simply a variation in which the propensity of the tumor cells for basal lamina production is pronounced.

Such a pattern of cellular differentiation and organization has been defined for pleomorphic adenomas[40,41] and adenoid cystic carcinomas[42,45] and is further evidence for a close histogenetic relationship of these tumors to salivary gland basal cell adenoma. Such a relationship was also apparent in a recent report of an unusual adenoma of parotid salivary gland.[49] These findings indicate the necessity for reassessing hypotheses attempting to define distinctive or separate types of progenitor cells for each of these three neoplasms.

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