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On the Differential Diagnosis of Clear Cell Tumours of the Head and Neck

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Clear cell tumours, both benign and malignant, derive from a diverse group of epithelial cell types including renal epithelium, keratinising epithelium, cutaneous adnexa, salivary glands, odontogenic epithelium, melanocytes and even mesenchymally derived cells of adipose and tendon sheath. In the head and neck, clear cell tumours represent a singular challenge to the pathologist since the classic morphological features of malignant neoplasia exemplified by cytological atypia are frequently absent in malignant clear cell variants, thereby excluding reliance on this histopathological hallmark for the establishment of a diagnosis. The differential diagnosis of both benign and malignant clear cell tumours must take into account patterns of growth as well as the phenotype of accompanying cell populations when attempting to arrive at a definitive histological diagnosis. In this review article, the histopathology of head and neck tumours that harbour significant clear cell populations will be compared and contrasted.
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INTRODUCTION

TUMOURS COMPRISED of clear cell populations are usually of epithelial origin although melanocytic and mesenchymal neoplasms may include such cells. With a few exceptions, most neoplasms with clear cell populations also harbour additional cellular elements with phenotypic characteristics that allow for differentiation between them. Renal cell carcinoma, or hypernephroma, is the pillar of the clear cell tumour community and may be composed almost exclusively of vacuolated "vasser" cells [1–4]. Typically, the clear cells are arranged in diffuse sheets with sparse stroma; cytological atypia is frequently lacking (Fig. 1). It is axiomatic that when a homogenous clear cell tumour is located in the head and neck, metastasis from the kidney must be considered before concluding that such a lesion is primary.

Primary clear cell tumours of the head and neck, both benign and malignant, are rare and can be derived from a wide variety of tissues. Certain cutaneous epithelial and adnexal tumours may harbour or be dominated by clear cells, although most have unique histological features [5–20]. Clear cells are also commonly encountered in certain naevi and melanomas [21–25]. Many salivary gland tumours contain mucous secreting cells that appear to be clear or vacuolated, yet such cells will show positive staining with histochemical stains that identify both neutral and acidic mucosubstances. Other salivary tumours characteristically contain clear cell populations that do not stain for mucins [26–45]. Odontogenic tumours usually emulate normal stages of odontogenesis yet rare variants may be biphasic, composed of both clear cells and accompanying non-clear-cell populations that do not exhibit any resemblance to tooth germ elements [46–56].

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When clear cells predominate, a definitive diagnosis may be problematical since many of these tumours will share histological features. Indeed, the segregation of benign from malignant neoplasia may be obfuscatory. In this article, clear cell tumours that arise in the head and neck will be reviewed and the cellular nuances that characterise each entity will be discussed.

TUMOURS OF KERATINOCYTE AND SKIN ADNEXAL ORIGIN

Surface epidermal and cutaneous adnexal tumours are common on the facial skin. Both squamous and basal cell carcinomas have been reported to manifest clear cell variants and 90% of such neoplasms are located on the skin of the head and neck [5–7]. The tumour cells are arranged in islands and sheets with unmistakable origin from the surface. Although individual islands may be composed exclusively of clear cells, neighbouring cells will exhibit the typical features of either basal or squamous cell carcinoma. In basal cell carcinoma, the clear cell component is characterised by cells with vacant cytoplasm, distinct cell membranes without obvious desmosomal spines and round monomorphic nuclei (Fig. 2a). Conversely, the clear cell variant of squamous cell carcinoma contains cells with more atypical features including large pale oval nuclei and pleomorphism. The cytoplasm is rarely completely vacant, containing instead pale eosinophilic floccular or lacey material. Cell membranes are distinct and intercellular bridges may be evident. Usually, other islands in the tumour will exhibit the more typical features of squamous cancer including cytoplasmic eosinophilia, individual cell keratinisation and pearl formation. While reported as a cutaneous tumour, clear cell variants may arise from mucosal epithelium of the aerodigestive tract (Fig. 2b).

Certain adnexal skin tumours are characterised by clear cell populations including trichilemmoma, pale (clear) cell acanthoma, sebaceous gland tumours and both benign and

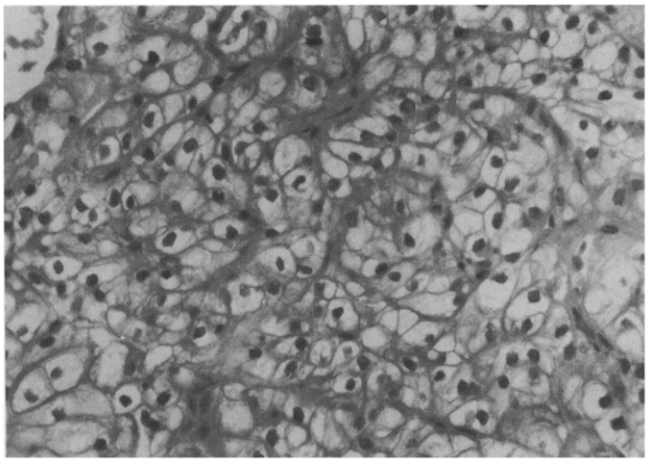

Fig. 1. Renal cell carcinoma, diffuse sheets of clear cells are traversed by thin septa (200×).

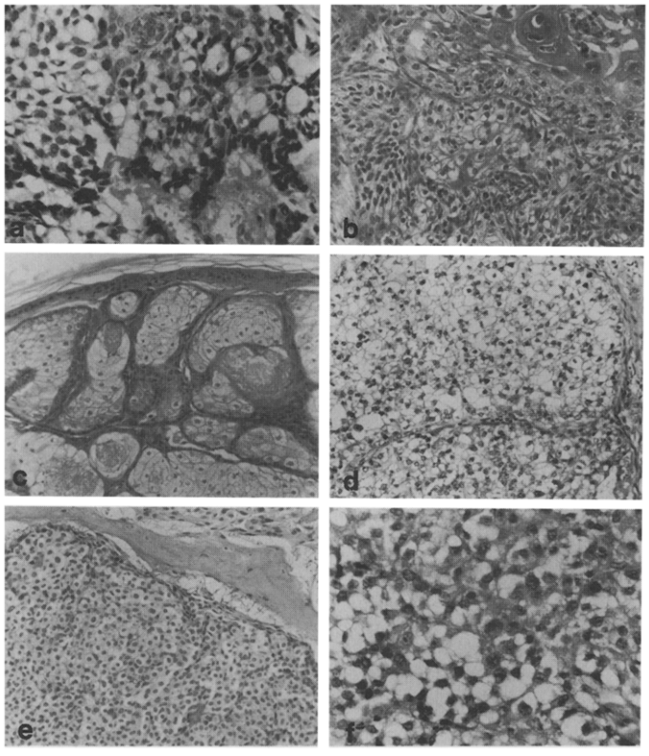

Fig. 2. Keratinocyte, adnexal and melanocytic tumours. (a) Clear cell variant of basal cell carcinoma (200×). (b) Clear cell variant of oral squamous cell carcinoma (100×). (c) Sebaceous adenoma showing lobular acini with characteristic sebaceous secreting cells (100×). (d) Clear cell syringoma with clear cell lobules and fine vascular septa (100×). (e) Clear cell hidradenoma (100×). (f) Clear cell variant of malignant melanoma with anaplastic nuclei (200×).

malignant tumours of eccrine origin [8–20]. Trichilemmoma is most often encountered on the face and neck and is derived from the follicular infundibulum where the upper hair shaft merges with the surface epidermis [8]. Multiple trichilemmomas are encountered in the Cowden syndrome being cutaneous markers of visceral fibrous hamartomas of the breast, gastrointestinal tract and thyroid with a heightened prevalence of breast carcinoma [9]. The tumour is benign and is characterised by bulbous acanthotic islands that extend into the papillary dermis yet maintain continuity with the surface epithelium. The islands are rimmed by basal cells and the spinous layer region is entirely or partially occupied by clear, vacuolated cells with monomorphic, centrally placed nuclei. The contiguous clear cells have defined cell membranes. Another pattern of growth is occasionally observed in that the acanthotic sheets of cells, while maintaining continuity with the surface, show anastomosing rete ridges that extend horizontally to form a plate-like pattern. Clear cells are clustered as foci within the acanthotic spinous layer that is bordered by palisaded basal cells. Hair follicles are seen to enter the lower aspect of the cellular plate and occasionally hair papillae-like structures evaginate from the lower strata. A similar appearance is seen in the clear cell acanthoma which also emanates from and maintains continuity with the surface [10, 11]. On close examination, the cells are faintly eosinophilic rather than completely vacuolated and leucocytes in a psoriasiform pattern are present; such lesions should not be confused with the neoplastic lesions discussed here.

Sebaceous adenomas and carcinomas are clear cell tumours in which the neoplastic epithelial nests are located in the papillary dermis yet may show continuity with the overlying epidermis. They are easily distinguished from other clear cell lesions by virtue of their characteristic cytosol. Surrounding a centrally placed nucleus, the sebum containing cytoplasm is notably multivacuolated, represented by a "soap-bubble" appearance in contrast to the large single vacant cytosol seen in the true clear cell tumours. The sebaceous adenoma maintains a pattern similar to that encountered in normal sebaceous and pilosebacous adnexa in that the vacuolated cells are arranged in alveoli with foci of squamous cells being compacted on the periphery of the alveolar islands, simulating the proximal segment of the sebaceous duct (Fig. 2c). It is noteworthy that multiple sebaceous adenomas and hyperplasias are associated with low grade visceral carcinomas, particularly of the intestinal tract in the Torre syndrome [12, 13]. Carcinomas with sebaceous differentiation also contain multivacuolated cells which tend to cluster into acinar-like configurations. The tumour islands of sebaceous carcinoma also show squamous differentiation yet unlike the benign sebaceous naevi and adenomas, cytologic atypia, particularly nuclear enlargement and pleomorphism, is clearly evident. In the head and neck area, any facial or scalp area may be the site of origin but far and away, origin from eyelid Meibomian glands is most frequent [14, 15].

Neoplasms of the sweat glands and ducts are classified according to the segmental level from which the tumours arise. The secretory glandular element resides deep in the dermis and connects to the intradermal eccrine duct that drains into the acrospiringium, the epidermal component of the sweat duct. Syringomas arise from the acrospiringium and are comprised of multiple ductal elements within the upper dermis that are lined by a double row of cuboidal cells. Tadpole or comma configured islands are common and the upper ducts may contain keratin. The clear cell variant shows oval sheets of vacuolated clear cells with sharply defined plasma membranes and dark monomorphic round nuclei (Fig. 2d). Some of these islands merge with true ducts. These clear cell islands may be rimmed by a thickened basement membrane [16, 17]. Eccrine spiradenoma is probably derived from the dermal eccrine duct cells and glandular cells [18]. A related sweat gland tumour showing similar histomorphology and also

derived from the ductal element of the gland is clear cell hidradenoma. This dermal tumour is typically painful and appears as a cutaneous nodule. The tumour grows as multilobular islands within the dermis, is not usually in continuity with the epidermis and a biphasic histological pattern is observed. The clear cells constitute the majority of the cell population and are well delineated from one another by distinct membranes. The nuclei are round, monomorphic and usually possess a single nucleolus. Traversing between the clear cells are tubular lumina lined by eosinophilic simple cuboidal or columnar cells. Rarely, in lieu of tubules are fusiform cells that run in streams. Occasionally, only clear cells are seen and the biphasic pattern can only be appreciated on further sectioning [19], (Fig. 2e). A malignant counterpart with metastatic potential has been described [20].

Cutaneous and adnexal clear cell tumours are not often confused with clear cell lesions originating in the salivary glands and jaws since the former lesions are clinically defined as skin nodules. Some maintain their continuity with the epidermis while others are located in the dermis. Regardless, the overall pattern of growth and the presence of other cell populations that are indicative of cutaneous derivation are usually present. Even the rare malignant variants of the adnexal tumours that contain clear cells are slow to metastasise.

MELANOCYTIC LESIONS

Normal melanocytes are clear cells located in the basal layer of skin as well as oral and nasal mucosa. Naevi are subclassified according to cell of origin (basilar melanocytes—nevocellular nevi, dermal melanocytes—blue naevi). Nevocellular naevi often contain cells with clear cytoplasm particularly in the junctional phase. A specific variant, the balloon cell naevus, is a nevocellular naevus with clear cytoplasm. There may be balloon cells in the junctional epidermis, yet most of the clear cells are arranged in lobules within the dermis. The lobules are in close apposition with ribbon thin intervening vascular septa. The clear cells show distinct membranes with small round, dark centrally placed nuclei. Differentiation from clear cell sweat gland tumours is not usually problematical since the peripheral cells of balloon cell naevus are often typically nevocytic. In addition, multinucleated clear cells may be evident and scattered melanin granules are generally identifiable in the upper aspects of the lobules [21, 22]. In superficial spreading melanoma, junctional clear cells with a Pagetoid appearance are commonly identifiable as they are in acral lentigenous melanoma. Nodular invasive melanomas may also be comprised of large clear cell populations and some of these neoplasms resemble balloon cell naevi with relatively innocuous appearing clear cells lacking pleomorphism (Fig. 2f). The accompanying epithelioid melanocytes betray this benign impression since these cells show cytologic atypia [23–25].

SALIVARY TUMOURS

Since many of the clear cell tumours discussed here share microscopic features, location and site of origin become germane to the diagnosis. Whereas metastatic disease must always be a consideration, location of a clear cell neoplasm in the major salivary glands or in the submucosa of the upper airway should conjure a preliminary diagnosis of salivary origin. Many salivary gland tumours contain mucus secreting as well as clear cells. The mucous cell component is basophilic and will stain positively with mucicarmine or alcian blue. The true clear cell tumours fail to stain positively for mucosubstances. These clear cell salivary tumours are differentiated from one another on a variety of histopathological nuances that will be detailed. With a few exceptions, most clear cell salivary tumours are malignant.

The epithelial–myoepithelial carcinoma of intercalated ducts is a clear cell tumour with a distinct, pathognomonic appearance. The tumour cells are arranged in large invasive lobules comprised of clear cells which are either oval or sometimes have a spindle, streaming appearance. The nuclei are oval or prolate and vesicular and are usually centrally placed in the clear cytoplasm. Characteristically, the clear cells surround tubular lumina composed of simple cuboidal ductal cells with eosinophilic cytoplasm and a glycocalyx (Fig. 3a). In many of these tumours, the lobules are comprised of organoid or acinar-like configurations in which the tubular ducts are enveloped by an outer clear cell rosette. This pattern resembles an intercalated salivary duct in which surrounding myoepithelial cells have transformed into clear cells [26–28]. As such, epithelial–myoepithelial carcinoma shares histopathological features with clear cell hidradenoma.

A very rare clear cell tumour that closely resembles clear cell syringoma and renal cell carcinoma is glycogen-rich adenocarcinoma. This tumour is comprised entirely of clear cells without other cellular elements that mimic salivary ductal or secretory components. Unlike renal cell carcinoma, the

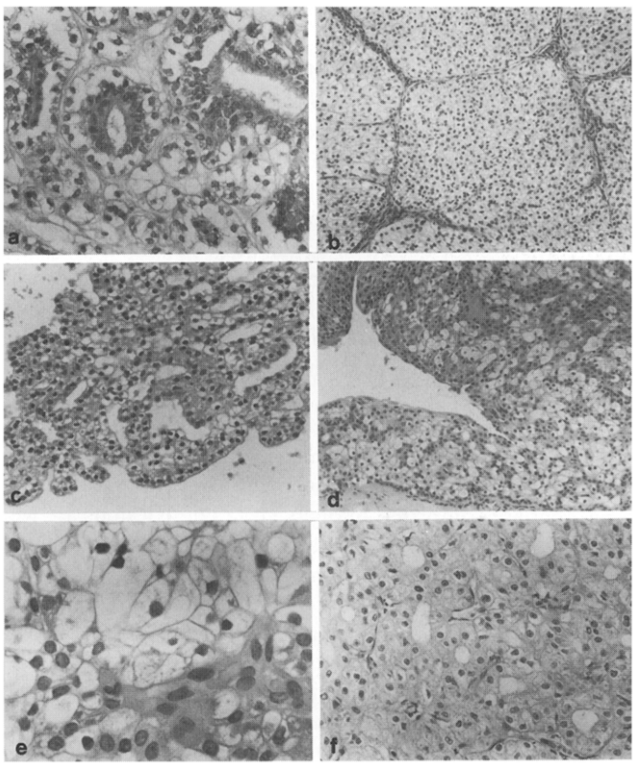

Fig. 3. Salivary tumours. (a) Epithelial–myoepithelial carcinoma of intercalated ducts showing characteristic peritubular clear cell arrangement (200×). (b) Glycogen-rich adenocarcinoma with lobules of clear cells rimmed by fine vascular septa (200×). (c) Acinic cell carcinoma with prominent clear cell elements (100×). (d) Mucoepidermoid carcinoma with a mosaic of squamoid cellular condensations and clear cells (100×). (e) Clear cells in mucoepidermoid carcinoma show distinct cell membranes (400×). (f) Clear cell oncocytoma retains the pattern of ordinary oncocytoma (200×).

cells are arranged in large confluent lobules and are strikingly monotonous. Only ribbons of capillary septa are evident (Fig. 3b). The margins of the lobules are relatively well delineated yet no capsule is encountered. Too few cases have been reported to ascertain their true behaviour although they are considered to represent low grade adenocarcinomas [29–31]. Indeed, some may be benign.

Acinic cell carcinoma exhibits a variety of patterns including microcystic, papillary cystic, solid organoid parenchymal, and follicular. Tumour cells rarely contain zymogen type granules; rather, they usually show large cytoplasmic volumes with faint basophilic or eosinophilic granules. Admixed with the acinar cells are clear cells and occasionally such cells will be present in large numbers (Fig. 3c). Regardless, other cell populations that are distinctly typical for acinic cell carcinoma are invariably present. In the regions of cystic change the luminally oriented cells show a hobnail or cobblestone surface, a feature very characteristic of acinic cell carcinoma [32, 33].

Mucoepidermoid carcinomas are graded into low, intermediate and high grade variants. All of the tumours under this designation are biphasic with a squamous cell and a mucous cell component. In addition, cells that appear to be a chimera of both types are commonly seen and are termed intermediate cells [34, 35]. Mucoepidermoid carcinomas may be solid with invasive tumour islands lacking cystic formations (high grade) or they may show large cystic spaces lined by papillary evaginations that are lined by columnar ductal cells and mucous goblet cells (low grade). A clear cell variant has been recognised and while other features of mucoepidermoid carcinoma are usually identifiable, some may be composed almost exclusively of clear cell sheets [36–40]. The clear cell variant of mucoepidermoid mucoepidermoid carcinoma is distinctive. The clear cells are arranged in confluent sheets and have distinct cell membranes with centrally placed monomorphic round nuclei. Delicate vascular septa divide the tumour sheets. The distinguishing feature, not seen in other clear cell tumours, is the formation of squamoid condensations primarily found around the periphery of the tumour islands and adjacent to the vascular septa (Fig. 3d, e). The clear cell variant of mucoepidermoid carcinoma is graded in the intermediate to high grade range implying a worse prognosis than low grade tumours.

Whereas it is not known if all instances of so-called glycogen rich salivary tumours are malignant, one type of salivary clear cell tumour is unequivocally benign. Oncocytomas are hamartomas that are comprised of oncocytes. These lesions are well encapsulated and the cells are arranged in acinar-like clusters or doughnut configurations with a small central lumen. In rare instances the typical eosinophilic, mitochondria engorged oncocytes undergo clear cell change [41]. In clear cell oncocytoma, akin to ordinary oncocytoma, the lesions are well encapsulated and show the same acinar or doughnut ductal clusters (Fig. 3f). Age associated diffuse and multifocal oncocytosis of the parotid is rarely clinically evident, although occasionally palpable hyperplastic foci appear. These multifocal adenomatous oncocytic hyperplasias may contain clear cell elements or may actually be comprised almost exclusively of pale or clear oncocytes [41–44].

A final entity to consider in the context of clear cell salivary tumours is primary malignant melanoma of the parotid gland. Whereas clear cell malignancies of renal or melanocytic origin could conceivably metastasise to the parotid region, it has been recognised that primary melanoma may arise within the substance of the parotid [45]. Some such tumours may contain large clear cell populations yet can be easily segregated from other salivary origin clear cell tumours since the melanomas are pleomorphic and contain melanin pigment granules.

ODONTOGENIC TUMOURS

Clear cells are frequently seen in certain benign odontogenic cysts and tumours such as gingival cysts, lateral periodontal cysts, botryoid odontogenic cysts and the epithelial islands of odontogenic fibromas. Such lesions are distinctive and would not be confused with other clear cell tumours. Alternatively, two odontogenic tumour variants contain large clear cell populations and may simulate metastatic renal cell carcinoma or other clear cell lesions. These include the clear cell variant of calcifying epithelial odontogenic tumour and the clear cell odontogenic tumour.

The calcifying epithelial odontogenic tumour fails to show any resemblance to normal odontogenic tissues. The epithelial neoplastic element is typically characterised by diffuse sheets or small islands of eosinophilic polygonal cells that often exhibit significant nuclear pleomorphism. The stroma contains zones of hyalinised material that stain for amyloid; laminated as well as dystrophic calcifications form in these hyalinised regions. In the clear cell variant, these same stromal elements exist and a few of the eosinophilic polygonal cells typical for this tumour may be scattered between the clear cells. The clear cell nests are usually small, forming acinar-like clusters (Fig. 4a). The basement membrane may be thickened or the cell islands may lie within a hyalinised stroma [46–50].

Clear cell odontogenic tumour is a recently described entity and is aggressive in nature [51–56]. Some cases have been reported to metastasise and it is possible that there are both benign and malignant varieties. The tumour is biphasic with clear cell islands of variable size admixed with solid islands and dental lamina-like cords of pale polygonal amphophilic

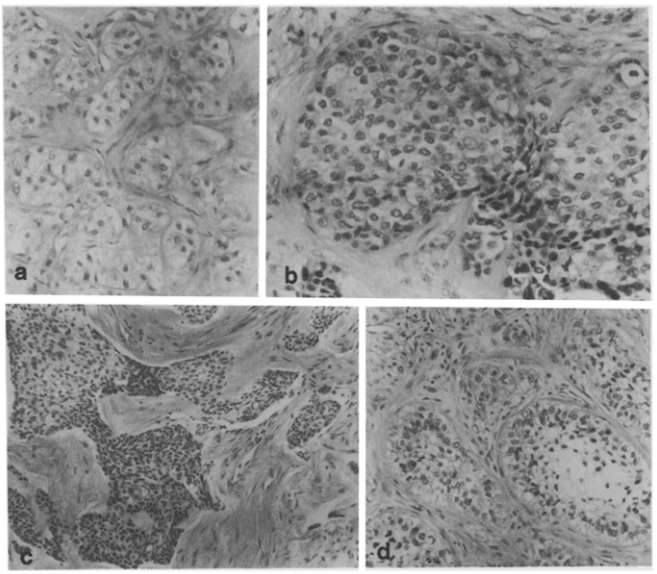

Fig. 4. Odontogenic tumours. (a) Clear cell islands within calcifying epithelial odontogenic tumour (200×). (b) Glomeruloid structures in clear cell odontogenic tumour (100×). (c) Biphasic cellular elements and mature fibrous stroma in clear cell odontogenic tumour (100×). (d) Attempts at peripheral nuclear palisading and nuclear atypia in clear cell odontogenic carcinoma (100×).

appearing cells that fail to show any squamous, glandular or ameloblastic features. The two cell populations often merge and the clear cell element blossoms about a stalk of the polygonal cells creating a "glomeruloid" pattern (Fig. 4b). As opposed to most of the other clear cell neoplasms that have very scant stroma, the epithelial islands of clear cell odontogenic tumour are separated from one another by a cellular fibroblastic stroma (Fig. 4c). The clear cells are usually not well demarcated by a plasma membrane and the pale nuclei are centrally placed round, oval or angulated without nucleoli. The polygonal cells have more hyperchromatic nuclei. As stated previously, ameloblastic features are usually lacking. Some examples, however, show a tendency for columnar orientation of the outer stratum of clear cells that rest against the basement membrane. The degree of nuclear pleomorphism and hyperchromatism is quite variable within these tumours and will probably prove to be significant in determining metastatic potential (Fig. 3d). Thus, the most distinguishing features of clear cell odontogenic tumours are the concomitant presence of both clear and amphophilic polygonal cells in most such tumours and separation of tumour islands by a mature, cellular fibrous stroma.

DISCUSSION

Although clear cell tumours share a cellular phenotype, most can be differentiated from one another on the basis of site of origin and identification of accompanying cell types or characteristic growth patterns. Figure 5 summarises the similarities and differences in growth patterns among certain clear cell tumours. On the basis of histopathological features alone, certain tumours may appear identical. Clear cell syringomas and glycogen-rich adenocarcinomas of salivary origin are nearly identical both in pattern of growth and cellular morphology. Both tumours grow in confluent lobular monotonous sheets with ribbons of capillary septa. Whereas renal cell carcinoma may be included in the differential diagnosis, it tends to have smaller islands of clear cells and the capillary septa are more extensive.

Clear cell hidradenoma and epithelial–myoepithelial carcinoma appear to be sweat gland–salivary gland counterparts. Both show tubular ducts surrounded by clear cells. While epithelial–myoepithelial carcinoma exhibits distinct peritubular blossoms of clear cells, the clear cells of hidradenoma are more sheet-like in appearance.

Most of the remaining clear cell tumours discussed here possess other cellular phenotypes that are encountered in their more classic presentations. Thus, both basal and squamous clear cell carcinoma variants have typical basal cell and squamous cell carcinoma foci. Likewise, most of the clear cell salivary tumours including acinic cell carcinoma, oncocytoma and mucoepidermoid carcinoma harbour recognisable patterns usually encountered in the classic forms of these neoplasms. The clear cell variant of mucoepidermoid carcinoma is an exception since it does not always contain classic mucous and epidermoid elements; however, the squamoid condensations interposed among clear cell clusters are notably distinctive.

Clear cell odontogenic tumour arises central in the jaws and can be differentiated from the clear cell variant of calcifying epithelial odontogenic tumour since the latter contains foci of hyalinised amyloid, calcifications and polygonal eosinophilic cell islands. Although mucoepidermoid carcinoma can arise centrally within the jaws, the histopathological features are, as just mentioned, unique. Ruling out metastatic renal cell carcinoma may be problematical. A helpful feature in diagnosing clear cell odontogenic tumour is the presence of two cell populations and separation of tumour islands by a mature, often cellular, fibrous stroma. It is always appropriate to rule out metastatic disease when clear cell tumours of the jaws are encountered since histopathological features alone are not always reliable, even for the most experienced pathologist.

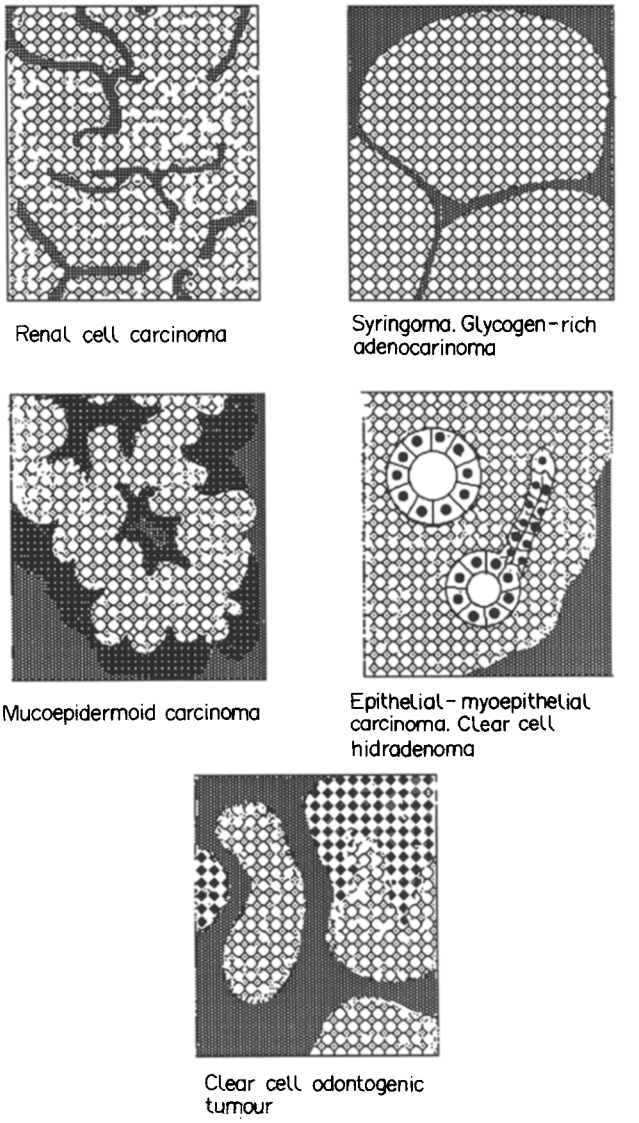

Fig. 5. Growth pattern similarities and differences among clear cell tumours.

The cytoplasmic vacuolisation in clear cell tumours, regardless of origin, can be attributed to glycogen accumulation. The glycogen is evident in fresh frozen sections stained with periodic acid–Schiff (PAS) reagent and, of course, is readily digested with diastase. The glycogen is solubilised during processing, leaving a clear cytosol in paraffin embedded tissues. Occasionally, fine PAS positive granules can be seen at the cytoplasmic membranes, yet this feature is not helpful in the differential diagnosis. There have not been any comparative studies on the use of immunohistochemical markers among the clear cell tumours. Ogawa and colleagues [31] investigated three clear cell salivary tumours, finding cytokeratin in all of them with variable results for vimentin, S-100 and actin. When melanoma is a consideration, monoclonal antibody

HMB45 should serve as a useful marker. Since most of the clear cell tumours discussed here are organelle-poor, it is unlikely that markers specific for cytoskeletal elements would prove to be diagnostically useful; nevertheless, such a conclusion cannot be drawn until controlled investigations are undertaken. In the meantime, a definitive diagnosis for clear cell neoplasms must be based on clinical and histopathological features.

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