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SPECIAL ISSUE: TOP TEN HEAD AND NECK DIFFERENTIALS

Top Ten Differentials to Mull Over for Head and Neck Myoepithelial Neoplasms

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Abstract

Background Myoepithelial neoplasms of the salivary gland are benign or malignant neoplasms composed exclusively of neoplastic myoepithelial cells. These tumors, including the benign myoepithelioma and the malignant counterpart myoepithelial carcinoma, exhibit a wide range of cytomorphologic features and architectural patterns.

Methods Review.

Results Myoepithelial cells can be epithelial, plasmacytoid, clear cell, spindle cell, and/or oncocytic cell, arranging as trabeculae, solid sheets, nests, cords, and/or single cells. A stromal component is commonly but not universally present, Therefore, their differential diagnoses are quite broad, including salivary gland neoplasms especially those with a myoepithelial component, plasmacytoma, melanoma, and various mesenchymal tumors.

Conclusion In this review, we summarize the characteristic histologic features, useful immunohistochemical panel, and common molecular alterations of myoepithelial tumors and their top differential diagnoses. A logical stepwise algorithmic approach and an immunohistochemical panel to include multiple myoepithelial markers are essential to establish the correct diagnosis.

Keywords Myoepithelial carcinoma · myoepithelioma · differential diagnosis · immunohistochemistry · molecular

Introduction

One of the most challenging categories in head and neck pathology is the group of myoepithelial lesions, whether developing in salivary gland sites or considering the differential diagnosis of epithelial-myoepithelial, polygonal, plasmacytoid, and spindled cells lesions which may demonstrate an overlapping immunohistochemistry phenotype. Core needle samples (usually radiographically obtained) provide a limited volume of material, generally lack a periphery, and oftentimes contain lesional tissue only without any clues to document anatomic site or possible tissue type. Clinical information given as "neck mass" or "soft tissue mass" aid little in narrowing the differential diagnostic considerations. In order to completely evaluate diagnostic possibilities, the employment of a logical, stepwise algorithmic approach to the differential diagnosis, combined with a targeted, but still comprehensive immunohistochemistry evaluation is necessary. Selected molecular studies may be included once the differential diagnosis has been narrowed, especially when the results of such studies provide therapeutic targets and not just confirmation of a diagnostic category. The goal of this review article is to discuss myoepithelioma and myoepithelial carcinoma of the head and neck mucosal and organ sites, along with discussion the pertinent differential diagnoses (Fig. 1) that should be considered and excluded through histology, histochemistry, immunohistochemistry, and potentially molecular studies.

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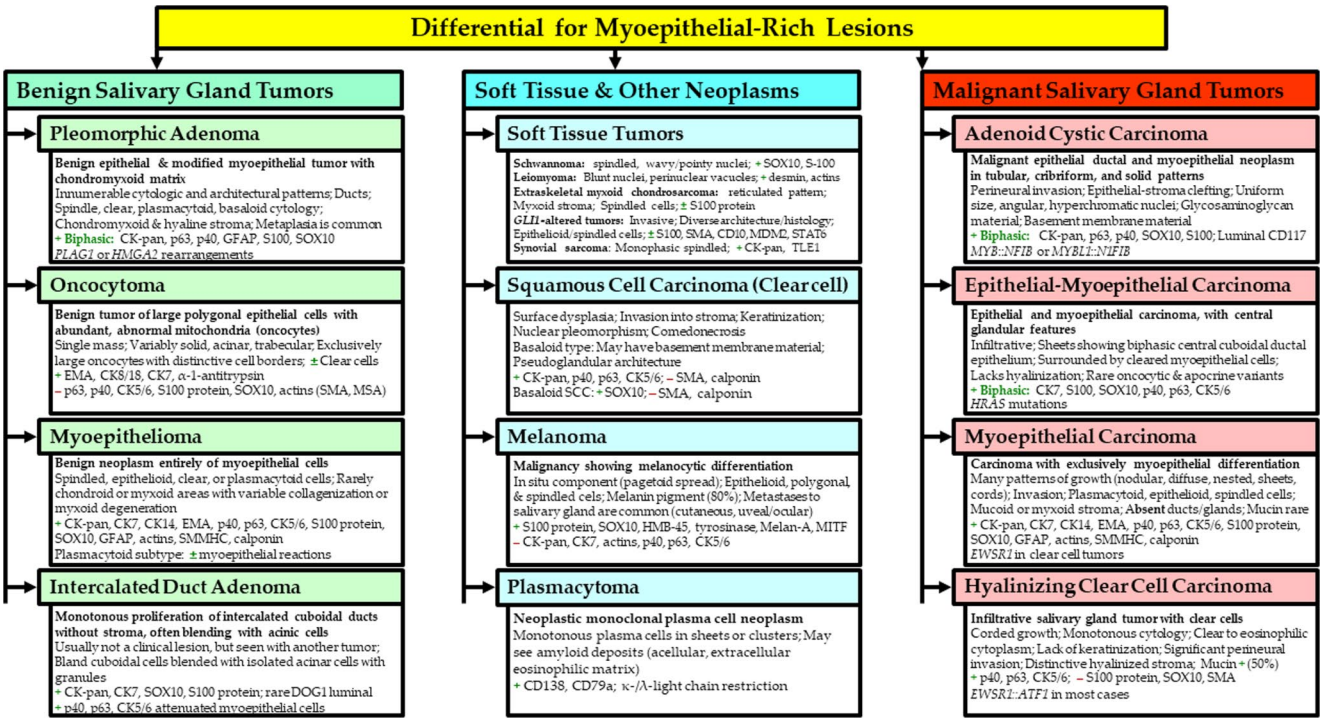

Fig. 1 Differential diagnoses for myoepithelial-rich lesions

Myoepithelioma and Myoepithelial Carcinoma

Myoepithelioma

Myoepithelioma is a rare benign salivary gland neoplasm composed entirely of myoepithelial differentiated cells without any discernible ductal component [1, 2]. As the name implies, destructive invasion, tumor necrosis, cellular pleomorphism and increased and/or atypical mitoses cannot be identified. As such a core needle sampling cannot access the periphery and is a factor that must be accepted as a limitation of the procedure type. In large series without referrable bias (i.e., cancer centers, large head and neck services), myoepithelioma comprises about 0.5 to 1% of all benign salivary gland tumors, about 0.3% of all salivary gland tumors, and usually identified in major salivary glands five times as often as minor salivary glands (still only comprising about 0.4% of all parotid gland tumors) [2–6]. Importantly, myoepithelial soft tissue tumors share overlap with salivary gland and mucosal site primaries, but generally have INI1 loss documented more commonly [7, 8]. Patients tend to be older (median 6th decade), with an equal sex predilection to slight male predominance [2, 5]. Recurrence is noted when there are positive surgical margins, while multiple recurrences may be associated with malignant transformation over time.

Tumors are well demarcated, but may not be encapsulated, usually < 3 cm (Fig. 2 A and 2B). There is an astounding range of appearances, from solid, myxoid, reticular, trabecular, nested, cord-like, net-like to packeted/alveolar. There may be interconnecting cords. There is usually a dominant pattern, but mixed appearances are also seen. The cells range from small to intermediate, with an epithelioid, spindled, plasmacytoid, or rhabdoid appearance (Fig. 3). There is an increased nuclear to cytoplasmic ratio. Nuclei are usually oval to round, appearing hyperchromatic, with spindled nuclei uncommon. The cytoplasm is more abundant in plasmacytoid or rhabdoid cells. There may even be a Hof zone adjacent to the nucleus, where there is cytoplasmic clearing. In general, the cytoplasm is lightly eosinophilic, but may be clear, vacuolated, oncocytic, or mucinous. The proliferation is set within a variably collagenized stroma, in which there is frequently acellular myxoid or mucoid stroma, without a chondroid appearance. Basement membrane-type material may be seen but a glycosaminoglycan material is absent. While controversial, duct or glandular structures should be absent [6, 9]. A very rare subtype contains intracellular mucin, a finding that broadens the differential with signet ring-cell tumors [10].

The neoplastic cells are variably reactive with a broad spectrum of both epithelial and myoepithelial antibodies which highlight a single cell population (i.e., all neoplastic cells show a similar reaction without a biphasic appearance). The cells are positive with pancytokeratin, AE1/AE3,

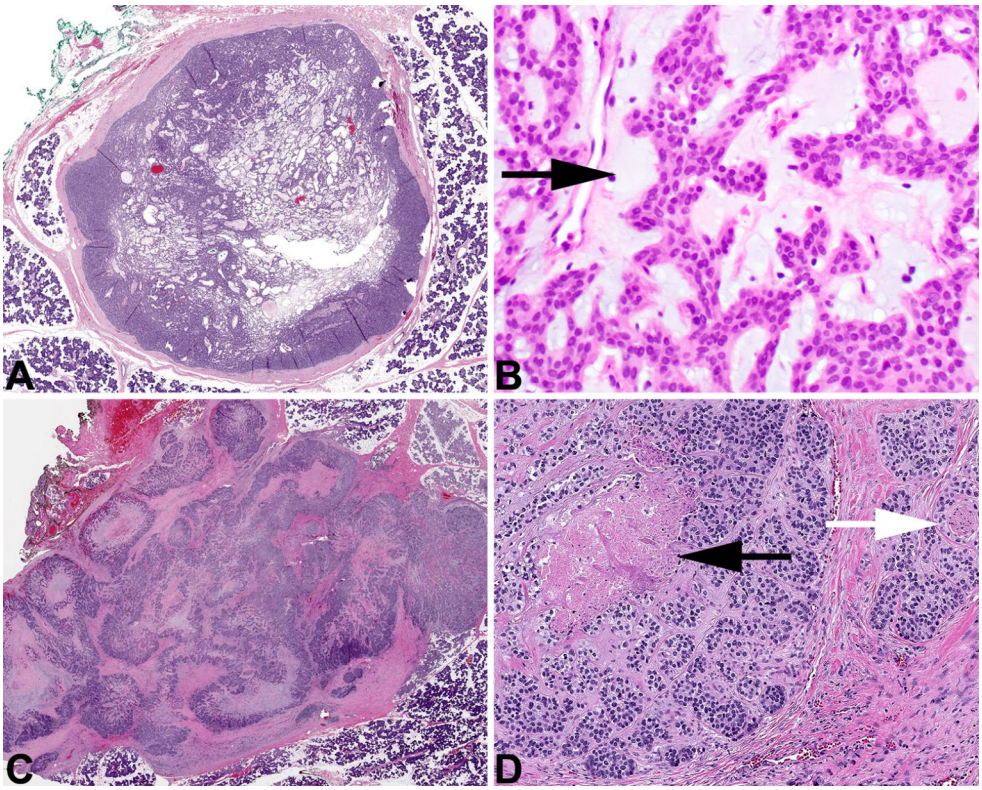

Fig. 2 Myoepithelioma (A-B) and myoepithelial carcinoma (C-D). **A** Myoepitheliomas are encapsulated and/or well-circumscribed showing no evidence of invasion. **B** There is often a myxoid (black arrow) to hyalinized stroma separating the tumor cells into cords or nests. **C** Myoepithelial carcinomas exhibit destructive invasion as expansile nodules or infiltrative nests. **D** Tumor necrosis (black arrow) and perineural invasion (white arrow) may be seen. Both tumor types are composed entirely of neoplastic myoepithelial cells

OSCAR, and CK7, while also reactive with myoepithelial markers which include CK14, SOX10, p40, p63, S100 protein, smooth muscle actin, calponin, smooth muscle myosin heavy chain, muscle specific actin and GFAP (Fig. 4). It is important to note that neoplastic myoepithelial cells may not react diffusely, strongly, or consistently with all the markers, and it is for this reason that several should be used as part of a panel in order to assure assessment of myoepithelial differentiation (pancytokeratin, SOX10, S100 protein, p40, SMA, and GFAP is a suggested initial panel). Further, actins and GFAP tend to be non-reactive in plasmacytoid myoepithelial cells [11]. DOG1 and GATA3 are usually negative in myoepithelial tumors [12].

Although seldom required, fluorescent in situ hybridization (FISH) for *PLAG1* may be detected, even though it is much more common in pleomorphic adenoma [13] while *EWSR1* rearrangements may be seen in clear cell myoepithelial tumors [14–16].

Myoepithelial Carcinoma

The malignant counterpart of myoepithelioma, myoepithelial carcinoma is composed exclusively of myoepithelial cells in a tumor with invasive growth (Fig. 2 C and 2D) [5, 6]. While there are histologic features that overlap, the soft tissue counterparts seem to be distinctive [7, 8]. Approximately 50% represent the carcinoma arising from a pleomorphic adenoma (carcinoma ex pleomorphic adenoma [CEPA]), while only rarely is there a precursor myoepithelioma. The tumor represents about 1% of malignant salivary gland neoplasms, while only about 0.2% of all tumors, predominantly in the major salivary glands (parotid >>> submandibular gland) [17–19], and usually in adults (only rarely reported in pediatric patients) [5, 20]. There is an equal sex distribution [5, 6, 17]. Clinically, especially in the CEPA setting, there is frequently rapid growth in a long-standing tumor mass. Tumors are usually regarded as intermediate to high grade, with frequent recurrences (40%), and regional metastasis (20%), usually later in the disease course [17, 21, 22].

The tumors may show a multinodular or bosselated surface, with cystic degeneration or necrosis noted only infrequently [5], often in larger tumors. Destructively invasive growth is the hallmark of separation from myoepithelioma, with perineural and lymphovascular invasion noted most often, and bone invasion seen infrequently. The histologic appearance overlaps myoepithelioma, although there is usually a higher cellularity, greater degree of pleomorphism, presence of tumor necrosis, and increased mitoses, including atypical forms. The same epithelioid, spindled, plasmacytoid, and cleared histologic features are seen, while the oncocytic or rhabdoid features are only rarely prominent [23, 24]. Pseudoglandular, pseudocribriform, or pseudoacinar structures may be seen. Basal lamina material may be present in the background myxoid to mucoid stroma [5, 25].

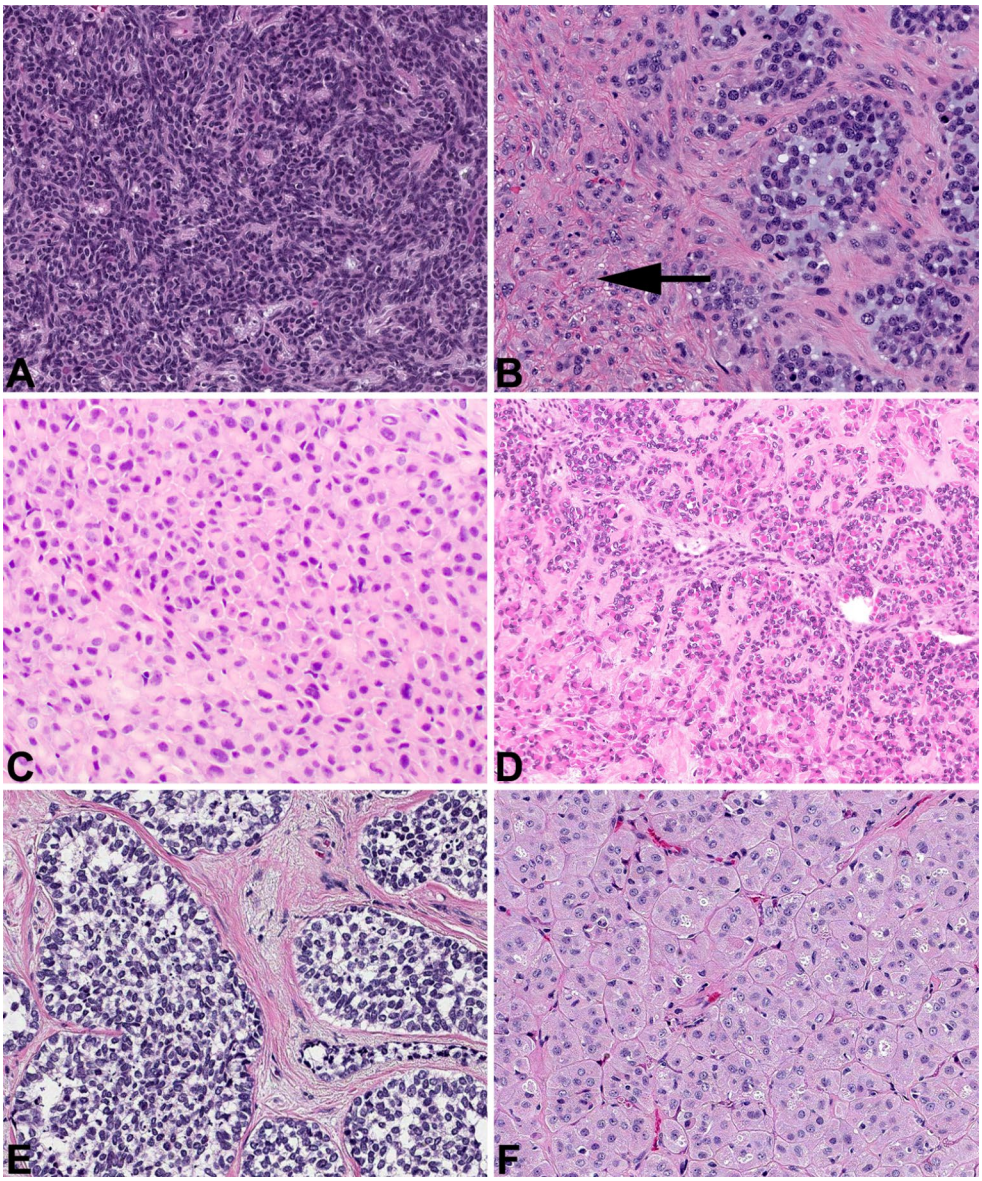

Fig. 3 Diverse cytologic and architectural features of myoepithelial neoplasms. The neoplastic myoepithelial cells may exhibit various cytologic features, including spindle cells (A), epithelial/epithelioid (B, black arrow), plasmacytoid (B, right and C), rhabdoid (D), clear cell (E), or oncocytic (F) features. The architectural patterns include solid sheets (A), single cells (B, black arrow), cords (B and D), trabeculae (E), and nests (B, E, and F)

Areas of benign PA may be seen in cases of CEPA [5]. In this setting, ducts within the PA may be identified. Clear cell pattern (often *EWSR1*-rearrangement associated) with squamous metaplasia and hyalinization may be seen, while squamous, chondroid, and rhabdoid differentiation is rare [26]. The secretory phenotype (mucicarmine-positive vacuoles) is exceptional [27]. Grading is proposed but is not standardized [5].

An immunohistochemistry panel helps with separation from sarcomas, but tends to support the myoepithelial differentiation of the single cell population only, without necessarily helping to place the tumor in a specific category: pancytokeratin, CK5/6, p63, p40, CK14, calponin, S100 protein, SOX10, and p53 overexpression [5, 6, 17, 28, 29]. When arising from a PA, *PLAG1* and *HMGA2* are commonly seen [30], with some unique fusions identified (such as *TGFBR3*::*PLAG1*) [5, 6]. Again, *EWSR1* rearrangements are more common in clear cell subtypes and are associated with a poor clinical outcome [6, 16, 24].

Differential Diagnoses

There are several lesions to consider in the epithelioid-plasmacytoid-spindled cell differential diagnosis that myoepithelioma/myoepithelial carcinoma raises, and these include benign and malignant salivary gland neoplasms, along with soft tissue tumors, melanoma, carcinoma, and even plasmacytoma. The top 10 considerations are presented briefly below, highlighting the unique or distinctive features which may aid in diagnosis (Table 1).

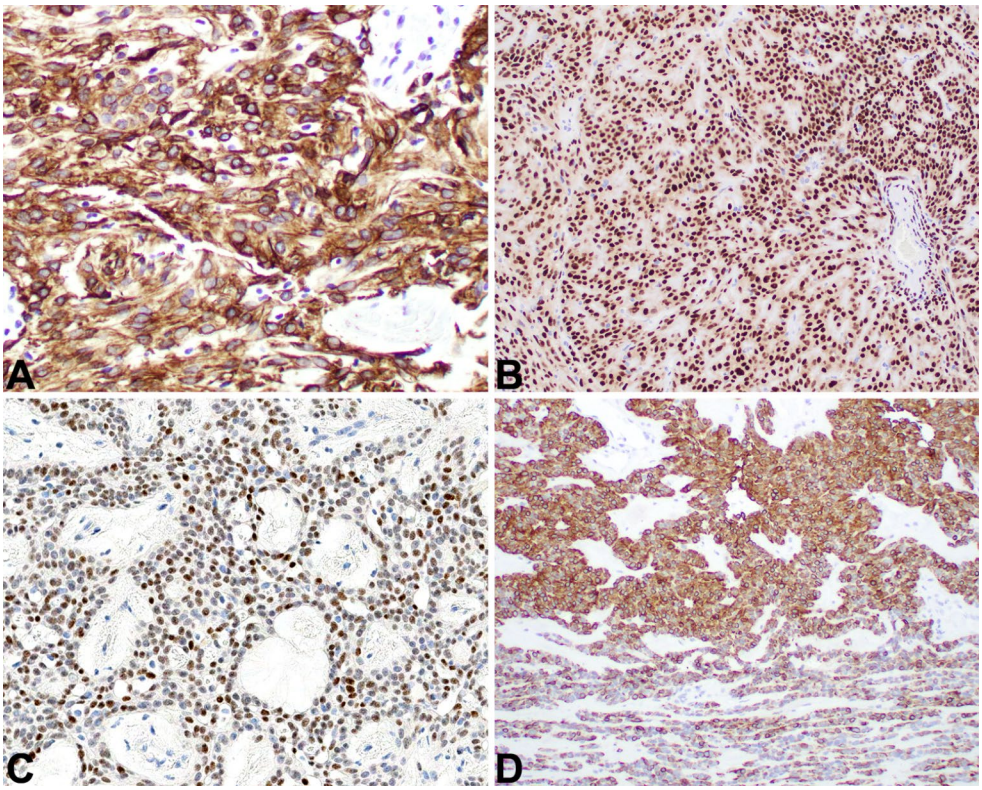

Fig. 4 Immunohistochemical profile of myoepithelial neoplasms. The tumors are composed of one cell type, commonly positive for CK-pan (A), SOX10 (B), p40 (C), and GFAP (D), among other antibodies, often in a patchy to diffuse, and weak to strong appearance, depending on the individual tumor

Benign Salivary Gland Tumors

Pleomorphic Adenoma

As the most common salivary gland neoplasm (both as a percentage of all tumors and of benign tumors), this benign epithelial (ductal), basal, and myoepithelial neoplasm with mesenchymal component (myxoid, chondroid, hyaline, osseous) must be considered. There is remarkable intra- and inter-tumoral diversity, which means that core needle or incisional biopsies may not adequately sample nor represent all of the histologic features of the tumor. Tumors most commonly affect the parotid gland, but 50% of all palate tumors are PA [31–33]. PA is also the most common second tumor when more than one tumor is present. In general practice, < 1% of tumors undergo malignant transformation, resulting in CEPA [34–36], even though often reported at a higher rate due to referral center bias. Complete excision is required to reduce the chance of recurrence.

The periphery is multinodular, bosselated and irregular, with filopodial extensions that bulge outwards. In minor salivary gland locations, a capsule is not seen. There is a remarkably variable histology, with many patterns of growth and many different cell types involved: as such, it is biphasic tumor with both a ductal and a myoepithelial component (Fig. 5 A). Specifically looking for ductal or tubular structures will help to separate the tumor from myoepithelioma. Notable, cellular PA may show very limited ductal differentiation with barely discernible lumen, while also showing limited to absent chondromyxoid stroma (especially in core needle samples). Metaplasias are common, with squamous, oncocytic, apocrine, and chondroid the most frequently noted. The neoplastic myoepithelial cells literally "melt" into the chondromyxoid background stroma without an abrupt edge or border. Heavy stromal hyalinization may be seen. Crystalloids (tyrosine, non-refractile collagenous or amianthoid fibers, oxalate-type) may be seen in up to 20% of tumors, but tyrosine crystals are usually not seen in myoepithelioma [37, 38]. The epithelial and myoepithelial cells may be spindled, clear, plasmacytoid, or basaloid. The most significant finding is the biphasic appearance, with ductal and myoepithelial cells [39]. This feature is accentuated with the epithelial and ductal cells more strongly immunoreactive with pancytokeratin, CAM 5.2, and CK7 while the myoepithelial cells are strongly reactive with SOX10, p40, p63, S100 protein, CK14, GFAP, SMA, SMMHC, and calponin [12, 40], while PLAG1 or HMGA2 immunohistochemistry may also be useful [41, 42], although not specific to pleomorphic adenoma. The most important consideration is the biphasic accentuation with these markers, a finding not seen in myoepithelial-only tumors. Thus, in general, myoepithelioma should have no ductal/tubular/glandular differentiation. Further, most tumors will show *PLAG1* or *HMGA2* rearrangements [43], but it must be recognized

Table 1 Immunohistochemistry panel approach to evaluate myoepithelial-type neoplasms

	CK-pan	p40	p63	CK 5/6	CK 14	S100 protein	SOX 10	SMA	Calponin	GFAP	HMB 45	TLE1	Other
Myoepithelioma/ Myoepithelial carcinoma	P	P	P	P	P	P	P	P	P	P	N	N	CK7, OSCAR
Pleomorphic adenoma	BI	M	M	M	M	BI	BI	M	M	M	N	N	PLAG1, HMGA2
Oncocytoma	P	P	P	N	N	N	N	N	N	N	N	N	Mitochondrial antigen
Intercalated duct lesion	BI	M	M	M	M	P	P	M	M	M	N	N	DOG1
Soft tissue tumors:													
1) Smooth muscle tumor	N	N	N	N	N	N	N	P	P	N	N	N	Desmin, SMMHC, caldesmon
2) Peripheral nerve sheath tumor	N	N	N	N	N	P	P	R	N	N	N	N	KBA62, H3K27me3
3) Extraskeletal myxoid chondrosarcoma	N	N	N	N	N	P	N	N	N	N	N	N	CD117, Syn, NSE
4) Synovial sarcoma	P	N	N	N	N	V	N	R	V	R	N	P	EMA, CD271, BCL-2, SOX9
Squamous cell carcinoma	P	P	P	P	N	N	N	N	N	N	N	N	
Mucosal melanoma	N	N	N	N	N	P	P	N	N	N	P	N	Melan-A, tyrosinase, MITF, PRAME
Plasmacytoma	N	N	R	N	N	N	N	N	N	N	N	N	CD138; CD79A; κ or λ
Adenoid cystic carcinoma	BI	M	M	M	M	P	P	M	M	M	N	N	CD117; MYB
Epithelial-myoepithelial carcinoma	BI	M	M	M	M	M	M	M	M	M	N	N	
Hyalinizing clear cell carcinoma	P	P	P	P	N	N	N	N	N	N	N	N	CAM5.2, EMA, CEA-m

BI: biphasic; P: positive; N: negative; M: myoepithelial/basal; V: variable; R: rare

SMA, smooth muscle actin; SMMHC, smooth muscle myosin heavy chain; GFAP, glial fibrillary acidic protein; Syn, synaptophysin; EMA, epithelial membrane antigen; NSE, neuron specific enolase; CEA-m, carcinoembryonic antigen-monoclonal; PRAME, PReferential expressed Antigen in MElanoma

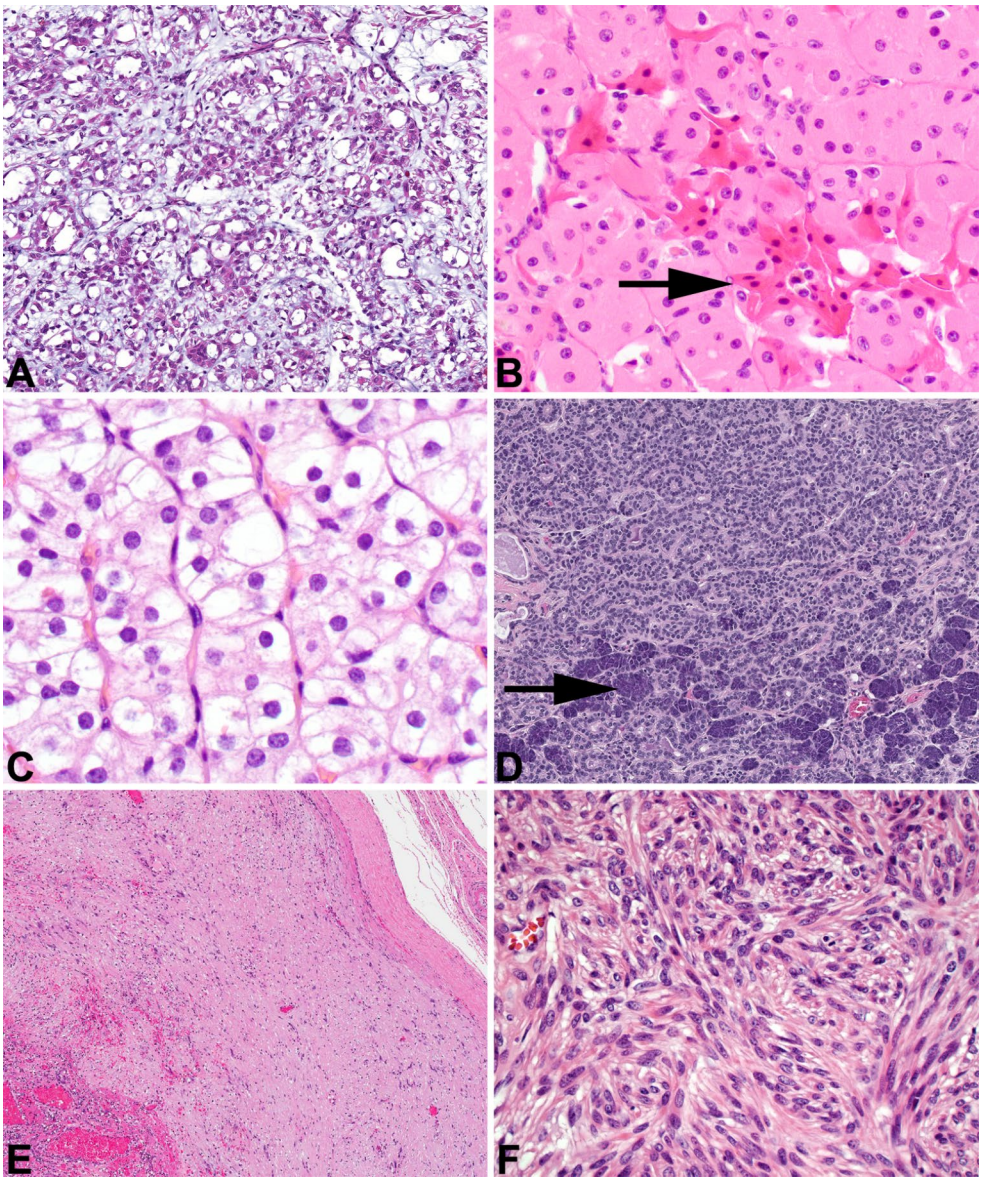

Fig. 5 Differential diagnosis of myoepithelial-rich lesions: **Benign neoplasms**. **A** A pleomorphic adenoma can be myoepithelial-rich. It is a biphasic tumor composed of ductal (epithelial) elements forming acini or microcysts surrounded by myoepithelial cells, set within a myxoid to chondromyxoid stroma. **B** An oncocytoma is a benign salivary gland neoplasm composed entirely of large oncocytes with abundant eosinophilic granular cytoplasm. Dark cells (black arrow) are sometime see in the tumor. **C** Clear cell change with prominent cell borders may be seen in some oncocytomas. **D** Intercalated duct hyperplasia/adenoma is a ductal proliferation of intercalated ducts lined by inner cuboidal ductal cells and outer myoepithelial cells, often blended with the adjacent serous acini (black arrow). **E** A schwannoma shows an encapsulated paucicellular spindle cell lesion showing degenerative nuclear atypia and hemorrhage (i.e., ancient schwannoma). **F** The interlaced fascicles of smooth muscle show blunt nuclei and perinuclear halos in this leiomyoma

that pleomorphic adenoma may be the underlying tumor in CEPA myoepithelial carcinomas [44, 45].

Oncocytoma

Myoepithelial tumors can be oncocytic, and as such oncocytoma must at least be considered. This benign neoplasm is composed exclusively of large polygonal epithelial cells with abundant abnormal mitochondria (oncocytes) and must not meet the criteria for another salivary gland type neoplasm. Oncocytoma nearly always affects the major salivary glands and in older adults (not children). Multinodular oncocytic hyperplasia may need to be separated from oncocytoma, but multifocality is not usually seen in myoepithelial tumors. The tumor cells are arranged as solid sheets, trabeculae or ducts, composed entirely of large cells with abundant, eosinophilic, finely granular cytoplasm with large central nuclei with prominent nucleoli (Fig. 5B). Cell borders are distinctive and thick. Light cells (oval vesicular nucleus) may alternate with dark cells (pyknotic nucleus; Fig. 5B), and basal cells may be seen, highlighted by p40/p63. The stroma is usually a delicate fibrovascular material, with stromal hyalinization or degeneration. Clear cells may be seen with abundant intracytoplasmic glycogen, although the granular eosinophilic cytoplasm is usually still present (Fig. 5 C). Phosphotungstic acid hematoxylin can be used to highlight the mitochondria, but anti-mitochondrial antibodies can also be used. The neoplastic cells are usually positive with pancytokeratin, CAM5.2, EMA and CK7, with basal cells highlighted by p40/p63/CK5/6 [46, 47]. There is a negative reaction with S100 protein, SOX10 [48], actins

(SMA, MSA), calponin, and GFAP, which helps to exclude the myoepithelial differential considerations.

Intercalated duct Lesions

Intercalated duct lesions, including hyperplasia and adenoma, are a ductal proliferation of bi-layered (epithelial and myoepithelial) intercalated ducts, usually identified incidentally in a gland removed for another reason. The parotid is primarily affected [49, 50]. There is a nodular to multinodular proliferation of cuboidal ductal cells with attenuated myoepithelial cells, frequently containing acinic cells (Fig. 5D). As a biphasic population, the epithelial (CK-pan, CK7) and myoepithelial populations (SOX10, S100 protein, p40, p63, SMA) are accentuated by their immunohistochemistry studies, while DOG1 highlights acinic cells [51].

Soft Tissue and Other Neoplasms

Soft Tissue Neoplasms (One Category, with Five Entities Considered)

Schwannoma

Schwannoma, a benign peripheral nerve sheath tumor composed of differentiated Schwann cells, usually shows a tumor eccentric to a nerve, showing cellular (Antoni A) areas of fusiform cells with wavy-buckled nuclei, which may be show nuclear palisading (Verocay bodies), alternating with myxoid/hypocellular (Antoni B) areas [52–54]. Vascular hyalinization is quite characteristic. Degenerative changes may be quite prominent (histiocytes, cyst formation, hemorrhage, Fig. 5E). The neural appearance is usually quite distinctive, and different from myoepithelial cells. The neoplastic cells are strongly and diffusely reactive with S100 protein and SOX10 [55], while keratins, SMA, calponin and other myoepithelial markers (p40, p63, CK14) are negative.

Leiomyoma

As a benign tumor of smooth muscle differentiation, a leiomyoma may mimic a myoepithelial tumor. However, the tumor is usually arranged in interlacing bundles or fascicles of neoplastic spindled cells that have blunt-ended to cigar-shaped nuclei, frequently associated with a perinuclear vacuolization [56–58] (Fig. 5 F). Vascular association or origin (angioleiomyoma) may be seen. Degenerative changes, especially mucinous or myxoid alterations may mimic myoepithelial proliferations. Fatty metaplasia may be seen, and is different from perivascular epithelioid cell (PEComa) tumors which co-express HMB45 and SMA. Tumor cells of leiomyoma are reactive with actins, desmin, SMMHC, calponin, and caldesmon, but are negative with pancytokeratin, p40, p63, S100 protein, SOX10, GFAP, and CK14 [59].

Extraskeletal Myxoid Chondrosarcoma

A tumor of uncertain histogenesis, this malignant soft tissue tumor often grows in a multinodular appearance, has uniform cells arranged in cords, clusters and a reticulated network within a background of abundant myxoid matrix. The histologic overlap with myoepithelial carcinoma is remarkable, and frequently, it is only the demonstration of the *NR4A3* fusion (with *EWSR1* or *TAF15*) that allows for a definitive classification. Within the head and neck, the orbit, sinonasal tract and oral cavity are most commonly affected [60, 61]. The long-term prognosis is about 58% at 15 years usually due to late metastases. The tumor is separated into nodules by fibrous septae, where the cords, clusters and trabecular of neoplastic cells are set within abundant pale-blue myxoid to mucinous stroma (Fig. 6 A). The tissue is hypovascular. The cells may have cytoplasmic vacuoles and the nuclei are uniformly round-oval with even chromatin. High grade tumors have more epithelioid neoplastic cells, with necrosis and increased mitoses. The immunohistochemistry phenotype is quite non-specific, showing variable S100 protein, CD117, synaptophysin and NSE reactivity, but generally showing a lack of muscle markers and GFAP. Pancytokeratin may be focally expressed [60, 62]. When there is a rhabdoid morphology, INI1 may be lost. In general, a break-apart FISH study for *NR4A3* helps to confirm the diagnosis [63].

GLI1-altered soft Tissue Tumor

This is a newly recognized molecularly defined mesenchymal neoplasm that demonstrates a mixed epithelioid and spindled morphology, but is defined by *GLI1* alterations. Gene fusions with *GLI1* are most common, but amplifications, occasionally with co-amplification of neighboring genes is seen in about a third of cases. About 40% of tumors develop in the head and neck (the tongue affected most commonly) [64–66]. Patients tend to be young adults without a sex predilection [66]. Invasive growth is common, especially protruding into vessels. The architecture and histology is quite varied, showing sheets, nests, fascicles, cords and reticular patterns, with small to medium cells showing epithelioid, ovoid and spindled shape, with clear to eosinophilic-amphophilic cytoplasm. The nuclei are round-oval and have small nucleoli. Mitoses are limited. The stroma is myxoid to hyalinized with a prominent vascularity of capillary-sized vessels (Fig. 6B) [64–66].

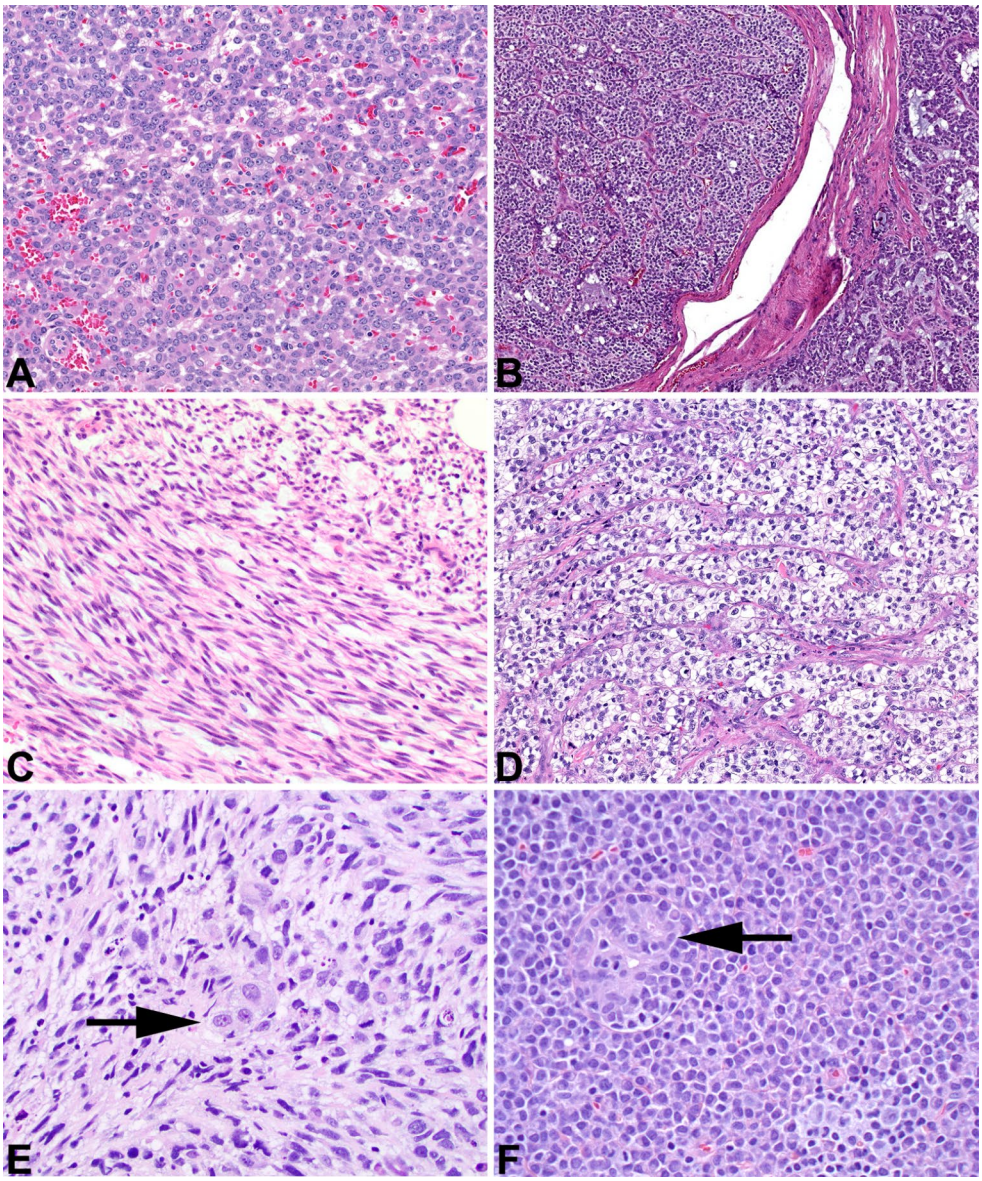

Fig. 6 Differential diagnosis of a myoepithelial-rich lesion: **Malignant neoplasms**. **A** Extraskeletal myxoid chondrosarcoma may show cords or bland epithelioid cells set in a loose myxoid stroma. **B** A mesenchymal tumor with *PTCH1*::*GLI1* fusion of submandibular gland contains epithelioid tumor cells with clear to eosinophilic cytoplasm arranges as nests separated by a delicate branching capillary network (left). Focal cord-like arrangement in a myxoid stroma resembling that seen in myoepithelial neoplasms is also present (right). **C** A monophasic spindled synovial sarcoma shows a syncytium of elongated spindled cells without any epithelial elements. Immunohistochemistry or molecular studies would be required to make a definitive diagnosis. **D** A metastatic clear cell squamous cell carcinoma lacks any easily identified squamous differentiation in this field. Other areas demonstrated more characteristic histologic features. **E** Metastatic melanoma shows both epithelioid (black arrow) and spindled cells in this focus. Nucleoli are prominent. **F** Marked plasmacytic differentiation is seen in this field of an extranodal marginal zone B-cell lymphoma, with a lymphoepithelial lesion (black arrow) aiding in the differential diagnosis

Immunohistochemistry is inconclusive, with patchy, weak or focal reactivity with smooth muscle actin, S100 protein, CD10, CD99, and epithelial membrane antigen, while usually negative with SOX10, HMB45, GFAP, CD34 and p63 [66–67]. When there is *GLI1* amplification, there may be concurrent immunohistochemistry overexpression of CDK4, MDM2, and STAT6 [66].

Synovial Sarcoma

Synovial sarcoma shows variable epithelial differentiation and is characterized by a specific fusion between *SS18* and *SSX1*, *SSX2* or *SSX4* genes [68]. Patients tend to be < 50 years of age at presentation, with head and neck tumors tending to be spindled monophasic tumors [69]. The tumor grows in a marbled, alternating light and dark pattern of cells arranged in short interlacing fascicles composed of spindled to epithelioid cells that form a syncytial arrangement. Mitoses are limited, necrosis is usually absent, and occasional mast cells may be seen. Calcifications may be present, but myxoid or mucinous stroma is usually absent. The neoplastic cells are usually positive with a nuclear TLE1 (Santa Cruz clone), with variable positivity with CD99, CK7, BCL2, and sometimes SMA and S100 protein in a focal distribution. Due to this type of inconsistent reactivity, using either SS18::SSX antibody E9X9V or the SSX-specific antibody E5A2C is highly sensitive and specific [70], while *SS18* FISH can also be performed in challenging cases.

Other Neoplasms

Squamous cell Carcinoma

Especially in mucosal sites (minor salivary gland locations), squamous cell carcinoma (SCC) must be included in the differential diagnosis. This is especially the case when the cells have clear cytoplasm (Fig. 6D) or show a spindled morphology [71, 72]. Generally, however, origin from the surface can be demonstrated, even when much of the surface is denuded or ulcerated. Focal areas of keratinization, dyskeratosis or opacified, orangeophilic cytoplasm can be seen. Intercellular bridges may be focally identified or may be prominent. There is often a desmoplastic stromal reaction, while a myxoid or mucoid stroma is unlikely. Metastatic tumors may be more challenging, especially when they exhibit nearly exclusively clear cell change (Fig. 6D). There is a single cell population immunoreactive with pancytokeratin, OSCAR, CK7, CAM5.2, EMA, p40, p63 and CK5/6. Occasional cases will show SMA reactivity, but strong reactions with SOX10, S100 protein, MSA, calponin and CK14 are usually absent in SCC [71].

Melanoma

Spindle cell mucosal melanoma is a malignancy showing melanocytic differentiation. When junctional activity or pagetoid spread is noted within the surface epithelium, a primary tumor can be documented [73–75]. However, ulceration may obscure this feature in many upper aerodigestive tract tumors. Metastatic tumors to the salivary gland and associated lymph nodes, may also simulate a primary neoplasm in these sites [76]. The cells may have an epithelioid quality, usually have prominent nucleoli, and may show intranuclear cytoplasmic inclusions (Fig. 6E). When melanin cytoplasmic pigment is present it helps to confirm the diagnosis. However, strong reactions with SOX10 and S100 protein, if performed in isolation, may lead to the conclusion the tumor is a spindled cell melanoma, when, if a panel were performed that included pancytokeratin, p40, CK5/6, SMA, calponin, and/or CK14, the true nature of the myoepithelial neoplasm would be revealed [55, 75]. Since melanoma is recognized to show phenotypic infidelity or anomalous immunoreactivity to a wide histologic diversity in patterns and cytomorphologic appearances, testing the neoplastic cells for several immunohistochemistry antibodies that confirm the diagnosis with positive results and exclude other diagnoses by their negative reactions is of value.

Plasmacytoma

The monoclonal neoplasm of plasma cells usually shows a plasmacytoid appearance, a finding that can also be seen in myoepithelial-derived neoplasms. Extraosseous lesions are uncommon, but review of imaging findings may aid in reaching a diagnosis [77, 78]. Plasma cells are scattered, clustered or arranged in sheets. The cells will have eccentric round nuclei with a clockface chromatin distribution, and generally show a perinuclear clear region (Hof zone). Amyloid deposits, Russel bodies, and Mott cells may help in reaching a diagnosis [79]. The background stroma tends not to be myxoid, mucinous or hyalinized. When hematolymphoid malignancies involve the salivary gland primarily, lymphoepithelial lesions in the background may aid in interpretation (Fig. 6 F). The neoplastic cells will show a reaction with hematolymphoid markers including CD138, CD79a, CD38, with λ- or κ-light chain restriction, while negative with pancytokeratin, actins, SOX10, S100 protein, and p40 [80, 81].

Malignant Salivary Gland Neoplasms

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (ACC) is a biphasic epithelial ductal and myoepithelial neoplasm with a characteristic tubular, cribriform, and solid architecture (Fig. 7 A) and a basophilic matrix and reduplicated basement membrane material [82, 83]. While one pattern may predominant, especially in small biopsies, the biphasic nature of the neoplasm should allow for separation [84, 85]. Still, this can be a very challenging differential consideration in limited and core samples where ductal differentiation is absent and a solid, clear or myoepithelial rich component dominates. Some tumor cells may show cleared cytoplasm, and the myxoid stromal matrix material may be a mimic for myoepithelial neoplasm. However, the tumor shows epithelial to stromal clefting (Fig. 7B), usually lacks tumor cell spindling, and shows nuclei that are angular, hyperchromatic and "peg-shaped" [82, 85, 86]. The cribriform pattern and perineural proclivity are not seen in myoepithelial carcinoma [83, 86]. The biphasic epithelial & myoepithelial differentiation is supported by the same markers performed for myoepithelial neoplasm, except expressed in two distinct compartments of the tumor. Further, CD117 is usually seen in the central ductal or tubular cells [82, 87]. In exceptionally difficult cases, FISH studies for *MYB*/*MYBL1* could aid in confirming the diagnosis [88].

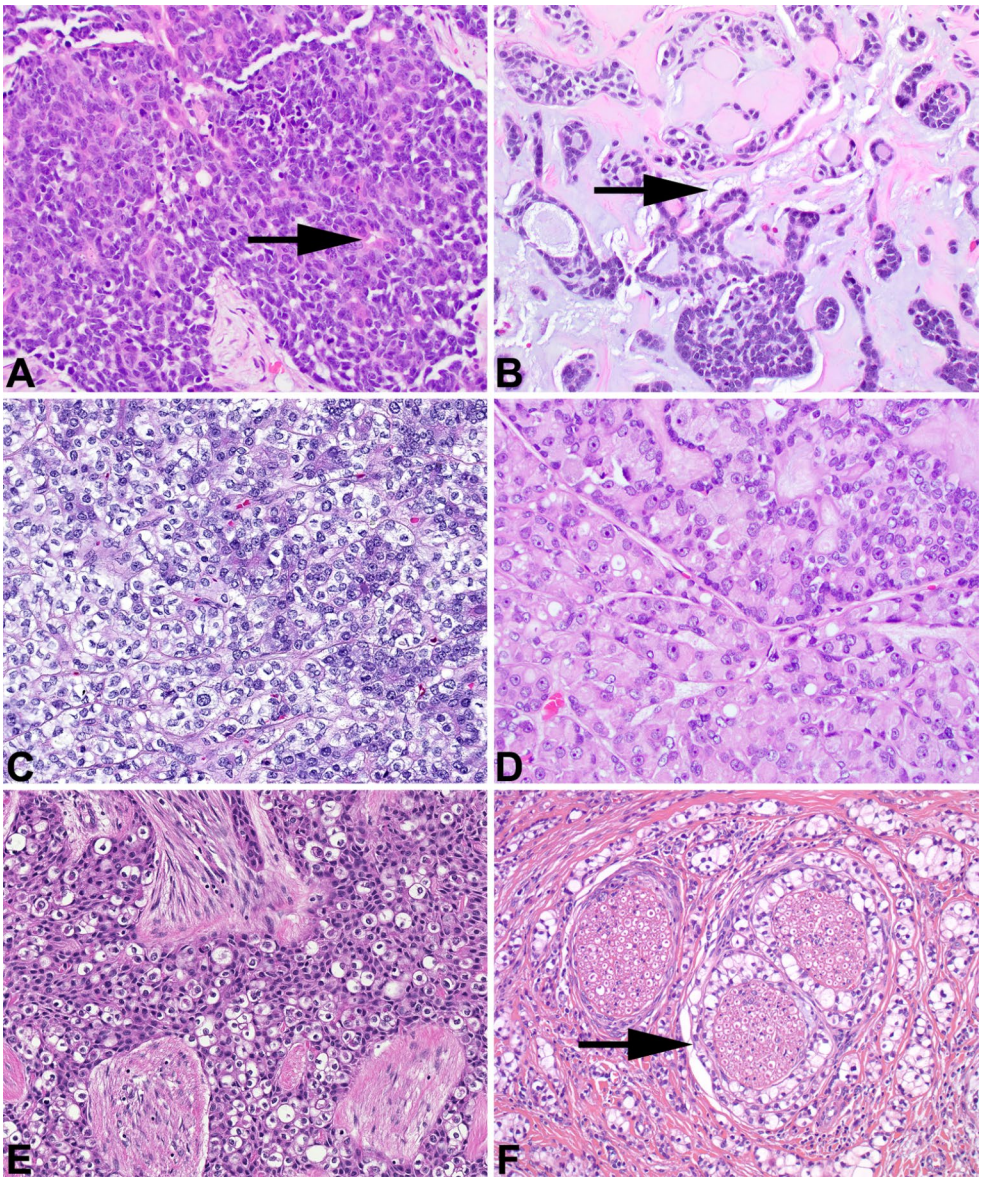

Fig. 7 Differential diagnosis of a myoepithelial-rich lesion: **Malignant salivary gland neoplasms**. **A** An adenoid cystic carcinoma (ACC) is a basaloid carcinoma composed of myoepithelial cells with dark angulated nuclei and ductal (epithelial) cells (black arrow) in this solid ACC. **B** Epithelial-stromal clefting is noted in this ACC (black arrow). There is a biphasic appearance of the neoplastic cells, separated by basement membrane and glycosaminoglycan material. **C** An epithelial-myoepithelial carcinoma (EMC) is a biphasic salivary carcinoma with inner ductal cells and outer cleared myoepithelial cells. **D** A prominent oncocytic morphology is seen in this EMC, although the biphasic nature is still noted (upper central). **E** A hyalinizing clear cell carcinoma (HCCC) of salivary gland is composed of tumor cells with clear or eosinophilic cytoplasm arranged as cord, trabeculae, nests and sheets in a characteristic hyalinized stroma. **F** HCCC frequently shows a very prominent perineural invasion (black arrow) by the clear cells

Epithelial-myoepithelial Carcinoma

Epithelial-myoepithelial carcinoma is a distinctive biphasic carcinoma, showing central tubular ductal structures surrounded by tightly coupled prominent outer myoepithelial cells (Fig. 7 C) [89, 90]. Again, as a biphasic tumor, it would be different from myoepithelial carcinoma. Still, in small samples, the central, tight ductal regions may not be histologically obvious, and many times are only highlighted by immunohistochemistry studies. The myoepithelial cells may predominant, and may be cleared or spindled [89, 90]. The oncocytic subtype is more difficult to recognize as biphasic, as often the oncocytic cells compress the lumen (Fig. 7D) [91. Generally, the luminal cells are highlighted by a stronger pancytokeratin and CK7, while the abluminal myoepithelial cells are highlighted by SOX10, S100 protein, p40, p63, SMA and calponin [90]. The myoepithelial/abluminal cells may also be reactive with RAS Q61R in a cytoplasmic or membranous fashion [92], recognizing the *HRAS* mutations that can help to confirm the tumor type [93].

Hyalinizing Clear cell Carcinoma

This low-grade salivary gland carcinoma composed of clear and eosinophilic cells arranged in sheets, cords, trabeculae, or nests set within a variably hyalinizing stroma is probably one of the most difficult to separate from myoepithelial neoplasms on H&E alone (Fig. 7E) [94–96], but only when myoepithelial tumors are clear cell type. The tumor affects minor salivary gland sites most often. The very dense, hyalinized basement membrane-like stromal component is probably the most helpful, although it is not always seen

in limited biopsy [96, 97]. The tumor cells show clear cytoplasm in the neoplastic cells, but not all cells have this feature. Still, a very prominent intercellular border is common (Fig. 7 F) [95]. Rarely, mucocytes and areas of squamous differentiation may be seen [96]. As a single cell population showing squamous differentiation, the cells will be positive with pancytokeratin, CK14, EMA, p63, p40, and CK5/6, but negative with myoepithelial markers SOX10, S100 protein, actins, and calponin [95]. As a clear cell tumor, it will show overlap with *ESWR1* rearrangements as seen in other tumor categories, although the fusion partner of *ATF1* in hyalinizing clear cell carcinoma is different, but not seen in all cases [15, 98, 99].

Conclusion

It is important to not be too "muscle-bound" when interpreting myoepithelial tumors of the head and neck and to instead consider a broad spectrum of epithelioid and spindled cell tumors that could show these changes. Consider the plasticity of the neoplastic cells in expressing both epithelial and myoepithelial markers in this single cell population neoplasm. A significant architectural diversity can be seen, while a remarkably variable cytomorphology can also be seen, set within a myxoid to mucinous stroma. Interpretation of the immunohistochemistry panel performed must consider the reactivity pattern within the tumor cells and the intensity and patchiness as well as whether it is a single cell or a biphasic tumor cell population. Invasion must be confirmed for a carcinoma diagnosis, recognizing the carcinoma may be part of a CEPA. When required for therapeutic options or differences in management, selected molecular studies can be added to confirm the diagnostic category.

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Declarations

Conflicts of Interest Both authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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