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Oncocytic salivary gland carcinomas

Ziyad Alsugair[1,2], Anne Champagnac[3] and Nazim Benzerdjeb[1,4,5]

[1]Department of Pathology, Institut de Pathologie Multisite, Hospices Civils de Lyon, Lyon Sud University Hospital, Pierre-Bénite, France, [2]Department of Pathology, King Abdulaziz Specialist Hospital, Taif Health Cluster, Taif, Saudi Arabia, [3]Department of Biopathology, Centre Leon Berard, [4]Université Claude Bernard Lyon 1, Lyon and [5]EMR3738, CICLY, Pierre-Bénite, France

Summary. Oncocytic carcinomas of the salivary glands represent a rare and diverse group of malignancies characterised by granular eosinophilic cytoplasm due to abundant mitochondria. This review provides a comprehensive overview of oncocytic salivary gland carcinomas, categorised by their morphological patterns: monophasic, biphasic, and complex. Monophasic entities include oncocytic intraductal carcinoma (OIDC), oncocytic salivary duct carcinoma (OSDC), acinic cell carcinoma (ACC), and secretory carcinoma (SC). These tumours vary significantly in histological architecture, immunohistochemical profiles, and genetic alterations, ranging from *TRIM33::RET* fusions and *BRAF* V600E mutations in OIDC to *NR4A3* rearrangements in ACC and *ETV6::NTRK3* fusions in SC. Biphasic tumours, such as oncocytic epithelial-myoepithelial carcinoma (OEMC) and oncocytic adenocarcinoma not otherwise specified (OANOS), further complicate diagnosis due to dual cellular composition and overlapping features with other neoplasms. Complex-pattern tumours, particularly oncocytic mucoepidermoid carcinoma (OMEC), highlight diagnostic challenges and underscore the need for advanced molecular diagnostics. This article emphasises the critical role of integrated histopathological examination, immunohistochemical staining, and molecular profiling in the accurate classification of these neoplasms. Despite diagnostic advancements, some entities, like OANOS, remain provisional, pending widespread access to transcriptomic tools. Recognising the molecular heterogeneity and clinicopathologic nuances of oncocytic carcinomas is essential for improving diagnostic precision, prognostication, and guiding targeted therapy.

Corresponding Author: Ziyad Alsugair, MD, Institut de Pathologie Multisite, University South Lyon Hospital-Hospices Civils De Lyon, 165 Chemin du Grand-Revoyet, 69310 Pierre-Bénite, France. e-mail: ziyad.alsugair@chu-lyon.fr

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Introduction

Oncocytic characteristics are a common feature of several salivary gland neoplasms, representing both benign and malignant entities (Capone et al., 2002). These oncocytic features, characterised by the presence of eosinophilic, granular cytoplasm, and a centrally located vesicular nucleus (Figs. 1A,B), are particularly prevalent in the head and neck region (Skálová et al., 1999). Distinguishing oncocytic changes from myoepithelial or apocrine alterations can be challenging due to overlapping features. However, a key differentiating factor lies in the ultrastructural findings. In oncocytes, mitochondrial hyperplasia is a hallmark, whereas in myoepithelial cells (historically referred to as hyaline cells, Fig. 1C), electron microscopy identifies longitudinally oriented fine filaments, approximately 4 to 6 nm in thickness. This distinction is critical for accurate diagnosis and classification, as it informs the underlying tumour biology and potential treatment strategies (Balachander et al., 2015). Apocrine changes typically present with a less expansive cytoplasm compared to oncocytic cells. The cells often exhibit a somewhat elongated appearance, with apical snouts (Fig. 1D) that can be observed within dilated cysts. These features distinguish apocrine changes from oncocytic alterations. The presence of apical snouts and the cystic nature of apocrine tumours further differentiate them from other glandular neoplasms, highlighting their distinct morphologic and functional characteristics (Song et al., 2023).

This review focuses on oncocytic carcinomas of the salivary glands, a group of malignancies that often elude precise classification due to their rarity and histopathologic overlap with other neoplasms. These tumours encompass a spectrum of morphologies and molecular profiles, highlighting the need for a

comprehensive understanding of their distinguishing features (Song et al., 2023).

Of particular importance is the recognition that oncocytic carcinomas may manifest in monophasic, biphasic, or other complex morphologies. Accurate diagnosis often requires a careful evaluation of histopathological features in conjunction with a specific immunohistochemistry panel and complementary molecular biology analyses. These integrative diagnostic approaches are essential for establishing precise classifications and informing effective treatment strategies (Vial et al., 2024).

Monophasic pattern

Oncocytic intra-ductal carcinoma (OIDC)

IDC is defined by the WHO as "a salivary gland malignancy that is characterised by papillary, cribriform and solid proliferations that are entirely or predominantly intraductal". IDC is a rare salivary gland tumour. It affects adults, with a wide age range from the 3rd to the 9th decades, and an even sex distribution (Brandwein-Gensler et al., 2004; Weinreb, 2011, 2018; Nakaguro et al., 2018; Skálová et al., 2019). IDC is most commonly a parotid gland neoplasm (WHO Classification of Tumours Editorial Board. Head and Neck Tumours, 2024). There are four subtypes: intercalated duct, oncocytic, apocrine and mixed, of which the intercalated IDC is probably the common type. IDC is a heterogeneous group of tumours, with a wide range of morphologic and genetic findings across the subtypes, but they are nearly exclusively low-grade, in situ tumours with a low potential for invasion, while in the apocrine type, it is not rare to recognise an invasive component (Fig. 2A,B). OIDC is characterised by ductal cells with typical eosinophilic granular cytoplasm and minimal nuclear atypia (Fig. 2C). These tumours may exhibit cystic features and display a variety of architectural patterns, including micropapillary, cribriform, and solid formations. As with all forms of IDC, they are characterised by a continuous myo-epithelial layer, which can be demonstrated through immunohistochemistry using markers such as p40 or p63 (Fig. 2D,E). Additionally, oncocytic and intercalated duct subtypes of IDC express S100 protein and SOX10 (Fig. 2F) (Nakaguro et al., 2018). The presence of a distinct myoepithelial layer surrounding tumour foci, highlighted by positivity for S100 combined with the positivity for SOX10 observed in oncocytes, provides important diagnostic clues, particularly because oncocytes do not typically express SOX10

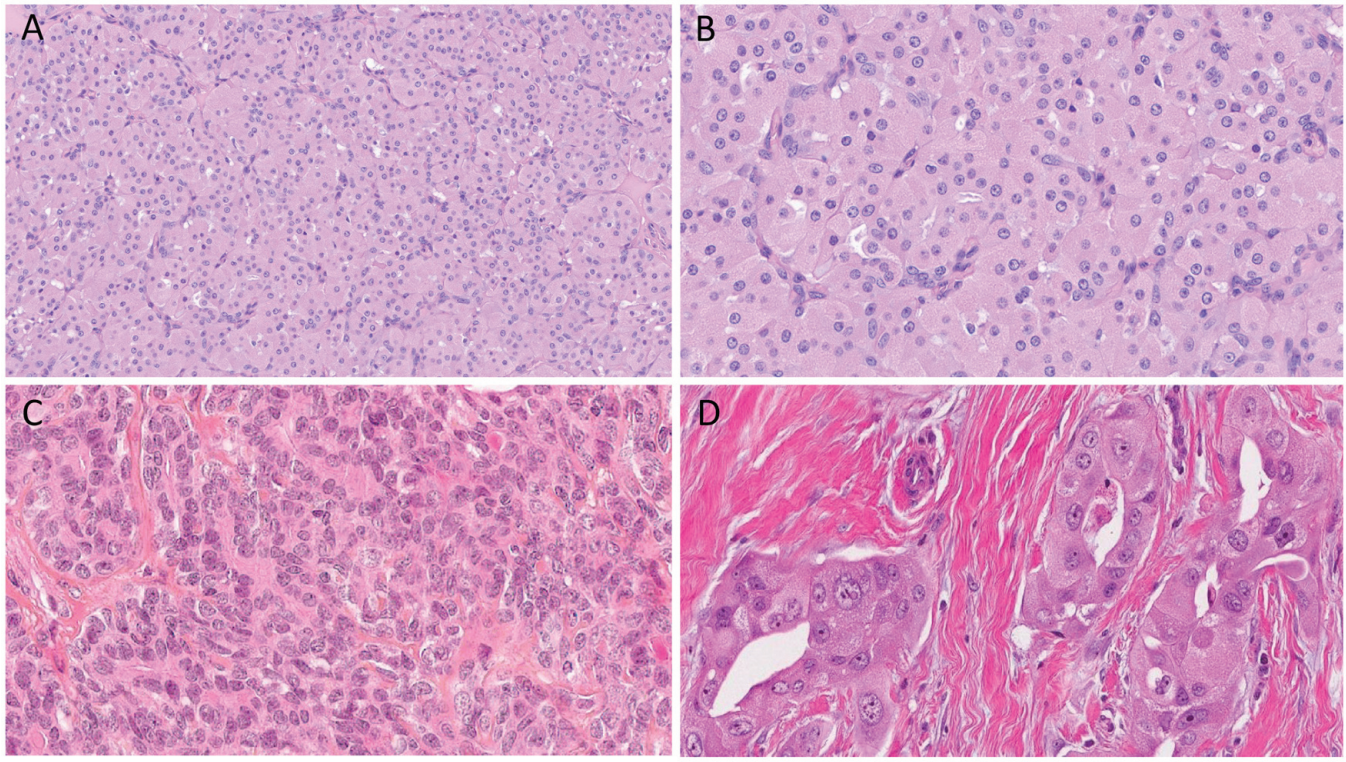

Fig. 1. Example of Oncocytic cells. Oncocytic proliferation arranged in cords and sheets **(A)**, oncocytes characterised by an abundant granular eosinophilic cytoplasm and centrally located vesicular nucleus **(B)**, myoepithelial cells (hyaline cells) characterised by longitudinally oriented fine filaments approximately 4 to 6 nm in thickness **(C)**. Apocrine cells typically present with a less expansive cytoplasm with apical snouts (or protrusions) **(D)**. A, x 20; B-D, x 40.

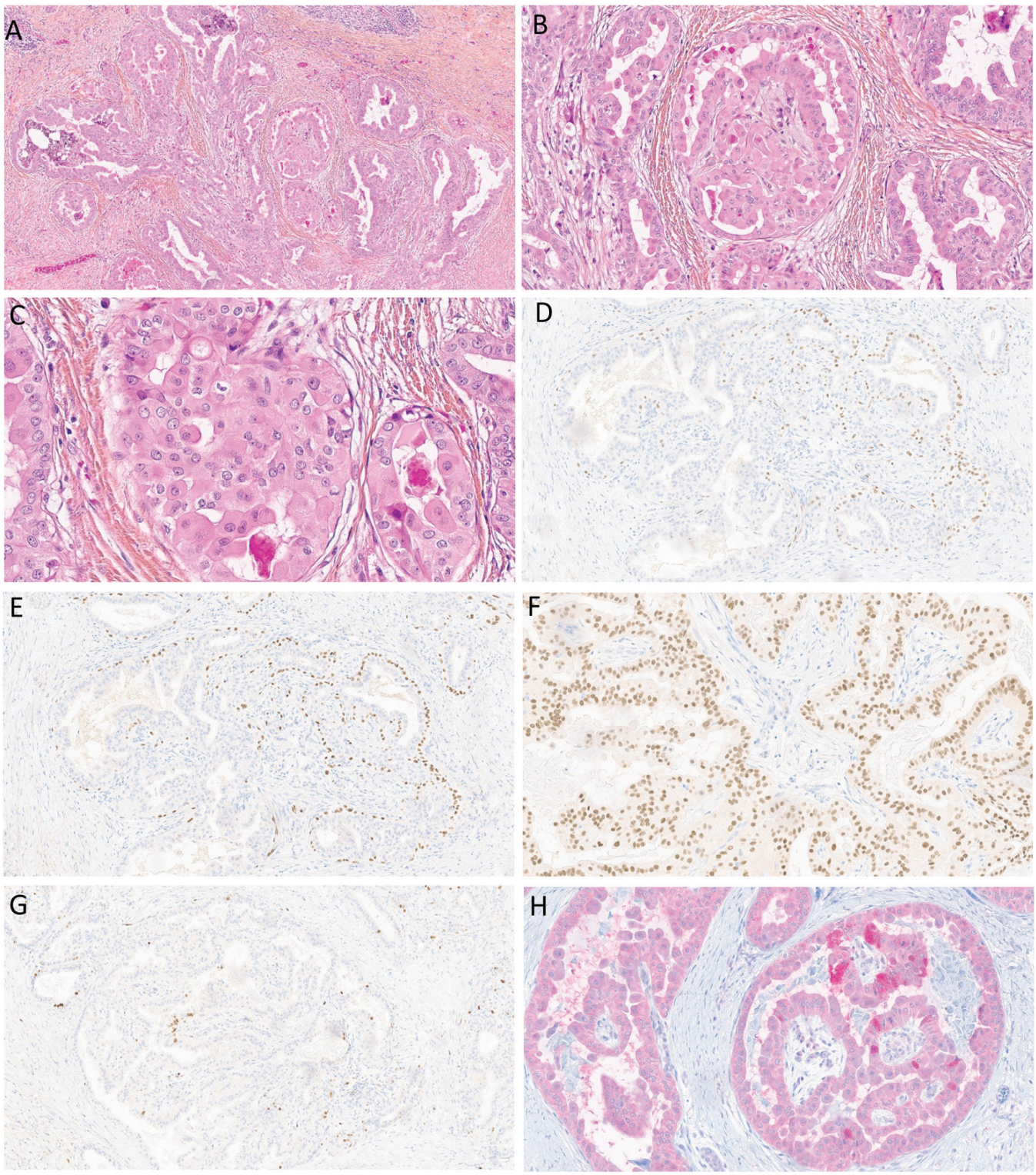

Fig. 2. Example of OIDC. Tumour proliferation is composed of an intraductal component of oncocytic cells **(A)**, which are characterised by intraductal oncocytic cells surrounded by fibrous tissue **(B)**. The oncocytic cells display a typical eosinophilic granular cytoplasm and minimal nuclear atypia **(C)**. The immunohistochemistry profile highlights a myoepithelial layer with positivity for p63 **(D)**, and p40 **(E)**; oncocytic cells with strong positivity for SOX10 **(F)**. The KI67 proliferation index ranges between 1 and 3% **(G)**. Some cases can harbour a BRAF mutation, highlighted by a cytoplasmic expression of BRAF V600E **(H)**. A-C, x 10; D-H, x 20.

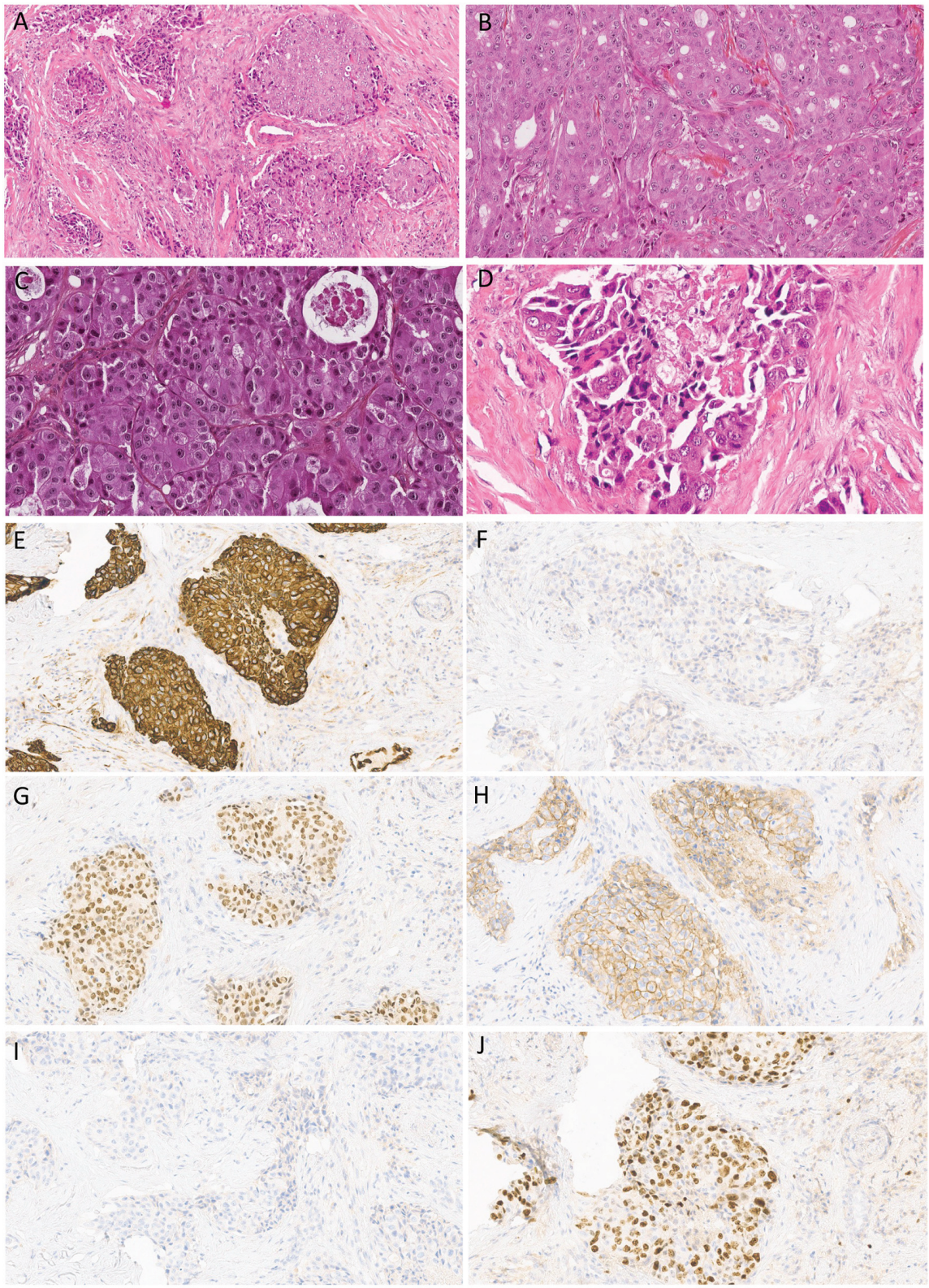

Fig. 3. Example of OSDC. This tumour proliferation displays more or less a large size of necrosis **(A)**, where OSDC comprises a cribriform pattern **(B)**. OSDC is composed exclusively of oncocytic cells **(C)**. The tumour cells are characterised by enlarged cells with abundant eosinophilic granular cytoplasm and a centrally placed nucleus **(D)**. The immunohistochemistry profile shows positivity for CK7 **(E)**; negativity for p63 **(F)**; in general, strong diffuse expression of the AR **(G)**; expression of HER2 **(H)**; and negativity for SOX 10 **(I)**. The KI67 proliferation index is elevated and exceeds 50% **(J)**. A, B, x 10; C, D, x 40; E-J, x 20.

immunostaining. This unique immunostaining profile challenges the traditional classification of these cells as oncocytes, which is currently based solely on their morphology (Skálová et al., 2019). In immunohistochemistry, androgen receptor (AR) and HER are consistently negative, and Ki67 levels are typically low, ranging from 1 to 2% (Fig. 5G). Molecular analysis has identified *TRIM33::RET* or *NCOA4::RET* fusions, as well as the *BRAF* p.V600E mutation, in OIDC (Fig. 5H) (Bishop et al., 2021). The rarity of these tumours presents significant diagnostic challenges, as their infrequency limits both clinical experience and data availability (Alsugair et al., 2024a,b; Bullock and Jiang, 2023). Nevertheless, pure IDCs of all subtypes, including OIDC, generally follow an indolent clinical course after complete surgical excision (Weinreb et al., 2018; Skálová et al., 2019).

Oncocytic salivary ductal carcinoma (OSDC)

SDC is an aggressive type of cancer that resembles high-grade mammary ductal carcinoma. Most tumours involve major salivary glands (van Heerden et al., 2003; Jaehne et al., 2005; Jayaprakash et al., 2014). SDC has a distinct male predilection and a peak incidence in the 5th to 7th decades of life (Williams et al., 2015). SDC is characterised by tumour cells with necrosis (Fig. 3A) and a cribriform pattern (Fig. 3B). Tumour cells exhibit large pleomorphic nuclei with prominent nucleoli and abundant eosinophilic cytoplasm (Fig. 3B) (WHO Classification of Tumours Editorial Board. Head and Neck Tumours, 2024), typically more cellular atypia and mitoses compared with breast carcinoma (Nakaguro et al., 2020). There are different subtypes of SDC, but they usually appear in combination with the typical features of SDC (Simpson et al., 2003; Nagao et al., 2004). An oncocytic subtype of SDC having more than 50% components shows oncocytic changes (Fig. 4C), which are characterised by enlarged cells with abundant eosinophilic granular cytoplasm and a centrally placed nucleus (Fig. 3D) (Simpson et al., 2003; Nagao et al., 2004; Sekhri et al., 2019). Immunohistochemistry shows positivity for CK7 (Fig. 3E), while the expression of p63 is negative (Fig. 3F) (Williams et al., 2015). A strong and diffuse expression of the AR is a characteristic feature of SDC (Fig. 3G), even if recent studies have shown its absence in 10% of cases (Di Palma et al., 2012). Positive staining for GATA3 or GCDFP-15 can also aid in the diagnosis (Williams et al., 2015; Sekhri et al., 2019) when the AR is negative in immunohistochemistry. Moreover, about 25-30% of cases have HER2 expression (Fig. 3H), although there is no consensus on reporting of HER2 in SDC, which can be observed even in the absence of AR. SOX10 (Fig. 3I) and S100 are usually negative. The Ki-67 proliferation index is elevated and exceeds 50% (Fig. 3J).

These genetic alterations are frequently associated with mutations in *HRAS* (23%), *PIK3CA* (23%), and *TP53* (55%). AR copy-number gain and splice variants have been identified (Mitani et al., 2014; Vial et al., 2024), as well as *ERBB2* gene amplification in SDC (Dalin et al., 2016). Furthermore, *PLAG1* or *HMGA2* rearrangements, which serve as markers of pre-existing pleomorphic adenomas (PAs), are observed in approximately half of SDC cases (Bahrami et al., 2013; Katabi et al., 2015; Chiosea et al., 2016). Given this biomarker profile, targeted therapies focusing on AR and HER2 have been developed as promising treatment options. However, despite these advancements, the prognosis remains poor, with five-year overall survival rates in cases involving regional lymph nodes and distant metastases limited to just 3-5 years (Johnston et al., 2016).

Acinic cell carcinoma (ACC)

ACC is a salivary gland carcinoma characterised by serous acinar differentiation without mucinous differentiation. ACC is a rare malignant tumour of the parotid gland, representing approximately 10% of all salivary gland malignancies, and up to 18% of parotid carcinomas (WHO Classification of Tumours Editorial Board. Head and Neck Tumours, 2024). The male-to-female ratio is 1:1.5 (Patel et al., 2014; Vander Poorten et al., 2016). ACC appears across a wide age range, with an average onset in the 5th decade (Vander Poorten et al., 2016). High-grade transformed ACC tends to occur about two decades later (Chiosea et al., 2012). The neoplastic cells in ACC are heterogeneous, predominantly comprising serous acinar cells, with vacuolated, intercalated, non-specific glandular (Fig. 4A), oncocytic, and rarely clear cells also present. ACC can exhibit a variety of architectural patterns, including solid, solid-lobular, acinar-microcystic, papillary cystic, tubuloductal (Fig. 4B), follicular, or macrocystic arrangements. Some tumours also show potential for dedifferentiation. The neoplastic acinar cells resemble the polyhedral cells of normal acini and are characterised by abundant, finely granular cytoplasm that may appear amphophilic, pale eosinophilic (Fig. 4C), or basophilic, with an eccentrically located nucleus (Fig. 4D). One distinguishing feature of ACC is the absence of basal or myoepithelial cells, which are not readily identifiable in routine sections. This necessitates immunohistochemical staining for accurate differentiation. ACC typically shows positivity for CK7 (Fig. 4E) and negativity for p63 (Fig. 4F). Additionally, immunohistochemical markers, including DOG1 (Fig. 4G), SOX10 (Fig. 4H), S100 (Fig. 4I), and CD117 (Fig. 4J), are positive in acinar and intercalated duct cells. Recently, nuclear staining for NR4A3 (NOR1) or NR4A2 (NURR1) has been observed in 98% and 2% of cases, respectively. NR4A3 immunohistochemistry has demonstrated high diagnostic utility, because of a sensitivity of 94.4% and a specificity of 99% (Haller et al., 2019b, 2020; Nguyen et al., 2020; Skaugen et al., 2021; Wong et al., 2021). In contrast to SC, ACC is typically negative for mammaglobin. Genetically, ACC is defined by a

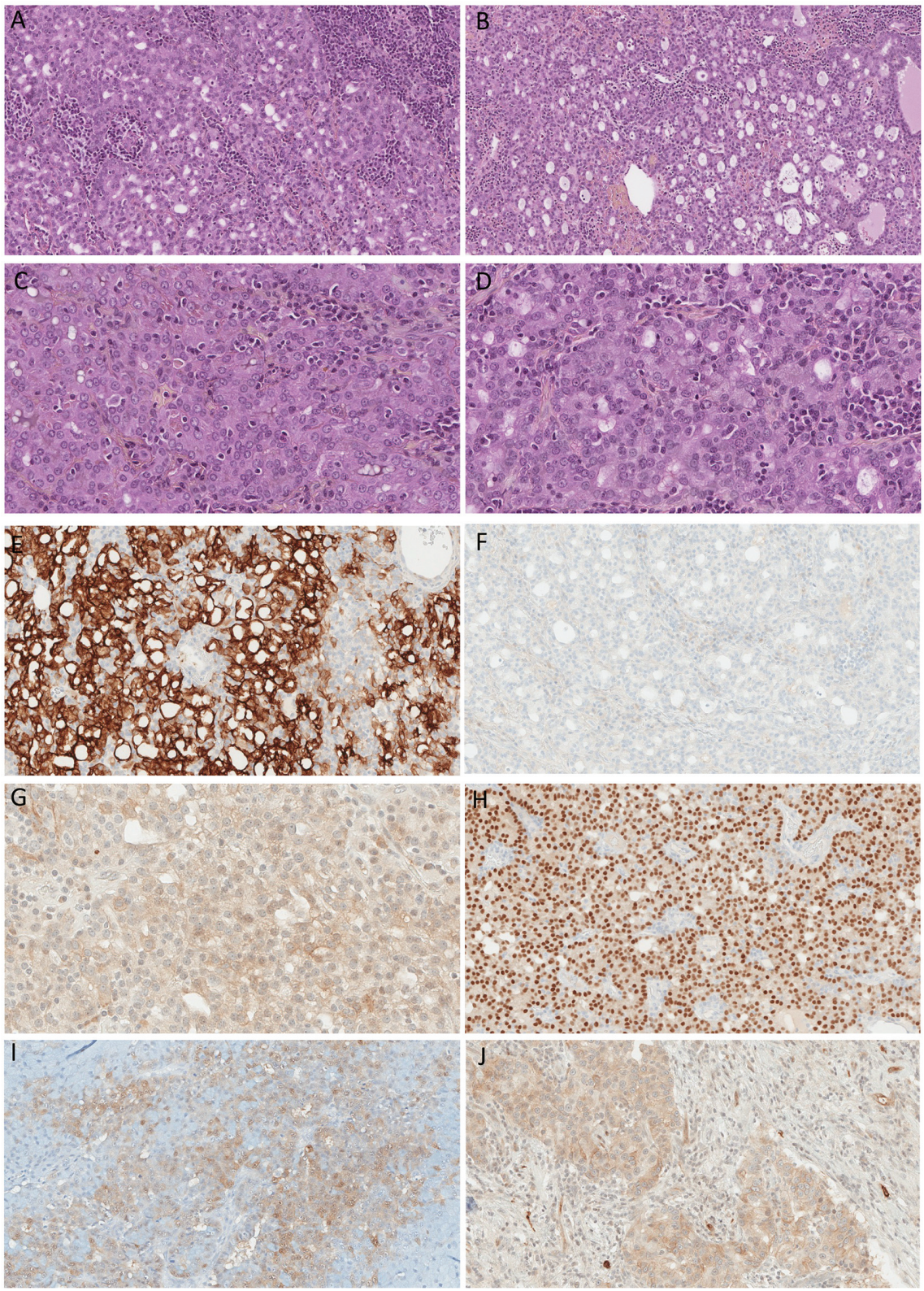

Fig. 4. Example of ACC. Tumour proliferation is composed of serous acinar cells, with vacuolated, intercalated, and oncocytic cells **(A)**, which can be arranged in a tubuloductal pattern **(B)**. The neoplastic acinar cells resemble the polyhedral cells of normal acini **(C)**. The oncocytic cells are characterised by an abundant, finely granular cytoplasm that appears amphophilic, pale eosinophilic, and an eccentrically located nucleus **(D)**. The immunohistochemistry profile exhibits positivity for CK7 **(E)**; negativity for p63 **(F)**; positivity for DOG1 **(G)** and SOX10 **(H)**; and heterogeneous positivity for S100 **(I)** and CD117 **(J)**. A, B, E-J, x 20; C, D, x 40.

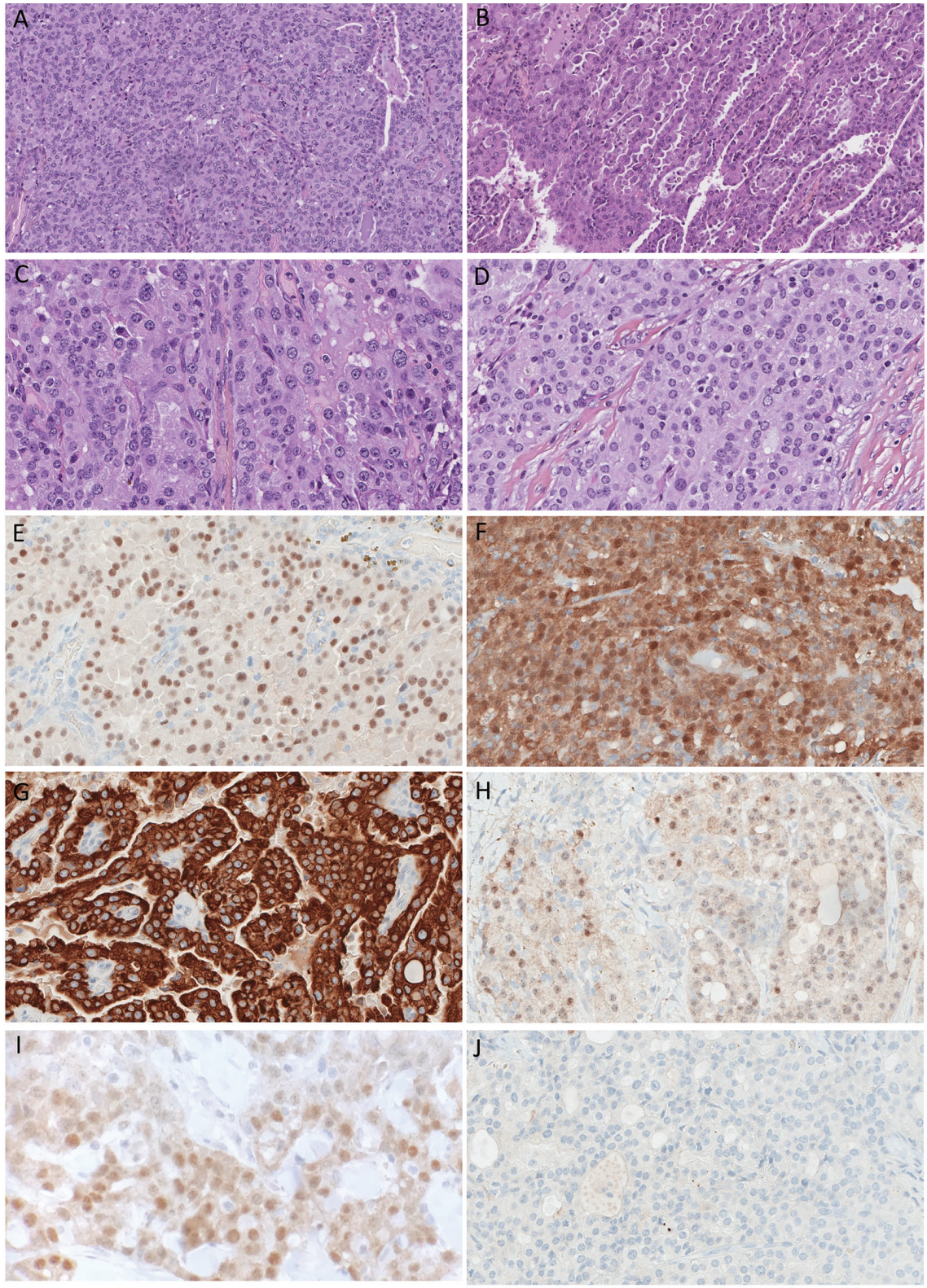

Fig. 5. Example of SC. Tumour proliferation is composed of compact sheets of oncocytic cells **(A)**, which are characterised by loosely cohesive clusters, sheets, and papillary structures **(B)**. The oncocytic cells are round to polygonal, with moderate to abundant cytoplasm containing vacuoles and fine cytoplasmic granules **(C)**. The nuclei are round to oval, with minimal irregularity and one to two prominent nucleoli **(D)**. The immunohistochemistry profile is diffusely positive for SOX10 **(E)**, S100 **(F)**, CK7 **(G)**; scattered peripheral positivity for p63 **(H)**; variable nuclear positivity of pan-TRK **(I)**, and negativity for DOG1 **(J)**. A, B, E-H, J, x 20; C, D, I, x 40.

characteristic t(4;9)(q13;q31) translocation, resulting in *NR4A3* (*NOR1*) gene rearrangement and upregulation (Haller et al., 2019a,b, 2020). More recently, a recurrent fusion involving the histatin 3 (HTN3) and Myb/SANT-like DNA-binding domain-containing 3 (*MSANTD3*) genes has been identified in 4-8% of ACC cases (Barasch et al., 2017; Andreasen et al., 2019). Clinically, ACC has relatively favourable outcomes, with 5- and 10-year survival rates averaging around 95% and 85%, respectively (Chiosea et al., 2012; Vander Poorten et al., 2016). However, distant metastases occur in approximately 20% of cases and significantly reduce survival rates to about 22% (Chiosea et al., 2012; Vander Poorten et al., 2016). Local recurrence rates vary by tumour grade, occurring in roughly 35% of conventional ACCs and up to 80% of high-grade tumours. Lymph node metastases are observed in about 10% of conventional tumours and 50% of high-grade tumours (Chiosea et al., 2012; Bury et al., 2016).

Secretory carcinoma (SC)

SC is a monophasic salivary gland carcinoma composed of cells with abundant eosinophilic or bubbly secretions, arranged in microcystic, tubular, and solid structures (WHO Classification of Tumours Editorial Board. Head and Neck Tumours, 2024). SC is a rare cancer typically occurring in adults, in the 5th decade and with an equal distribution between sexes (Skálová et al., 2010, 2013; Connor et al., 2012; Bishop, 2013; Baněčková et al., 2023). The most common site of occurrence is the parotid gland, followed by the oral cavity and submandibular gland (Skálová et al., 2010; Connor et al., 2012). Typically, this tumour presented as a painless, slow-growing mass. The cytomorphological features of SC may resemble those of other tumours, such as ACC and benign neoplasms of the salivary glands, making diagnosis challenging without ancillary studies. A definitive diagnosis requires histological examination and immunohistochemical analysis of the excised tumour. The cellular architecture of SC includes various arrangements, such as tight and loosely cohesive clusters, sheets, and papillary groups (Fig. 5A,B). Neoplastic cells are round to polygonal, with moderate to abundant cytoplasm containing vacuoles and fine cytoplasmic granules (Fig. 5C) (Griffith et al., 2013). The nuclei are round to oval, with minimal irregularity and one to two prominent nucleoli (Fig. 5D). SC shares similar growth patterns with ACC, but can be distinguished by its multivacuolated eosinophilic cytoplasm, presence of mucin, and absence of true zymogen granules. Papillary cystic architecture, which is rare in ACC, is more common in SC. Immunohistochemistry plays a critical role in the diagnosis of SC. SC is positive for mammaglobin, SOX10 (Fig. 5E), S100 (Fig. 5F), and CK7 (Fig. 5G). It also demonstrates scattered positivity for p63 (Fig. 5H) but is constantly negative for DOG1 (Fig. 5J), which contrasts with the opposite immunostaining profile seen in ACC (Chênevert et al., 2012). At the molecular level, SC is defined by a specific chromosomal translocation resulting in the *ETV6::NTRK3* fusion (Skálová et al., 2010; 2014). Interestingly, while this translocation is characteristic, panTRK immunohistochemistry may occasionally be negative, although some cases are positive (Fig. 5I). A small subset of cases shows divergent molecular findings, including alternate fusions such as *ETV6::RET* (Ito et al., 2015; Skálová et al., 2016; 2018), *ETV6::MET* (Rooper et al., 2018), *ETV6::MAML3* (Guilmette et al., 2019), and *VIM::RET* (Skálová, et al., 2020b). These variations highlight the molecular heterogeneity of SC. Clinically, SC is generally an indolent malignancy of the salivary glands. Recently, a proposed grading system for SC was developed due to its link to histologic findings and clinical behaviour. Although this grading system is not yet widely accepted, it could be recommended for use in the next WHO classification to help stratify risk and guide therapy (Baněčková et al., 2023). Lymph node metastases occur in up to 25% of cases (Sethi et al., 2014; Ayre et al., 2019), although distant metastases are rare (Boon et al., 2018; Baněčková et al., 2023). Despite its indolent behaviour, there are currently no predictive biomarkers for SC. However, the translocation status, particularly involving *ETV6::NTRK*3, may emerge as a potential predictive marker, especially as selective TRK inhibitors continue to be developed (Drilon, 2019).

Biphasic pattern

Oncocytic epithelial myoepithelial carcinoma (OEMC)

EMC is a rare salivary gland malignancy that comprises about 1-2% of all salivary gland tumours and 2-5% of malignant salivary gland tumours (Seethala et al., 2007; WHO Classification of Tumours Editorial Board. Head and Neck Tumours, 2024). EMC typically occurs in the 6th and 7th decades of life with a slight female predilection. This tumour can occur at essentially any site with major and minor salivary glands, including the lower respiratory tract, but has a predilection for major salivary glands, with 60-75% occurring in the parotid gland (Fulford et al., 2001; Doganay et al., 2003; Seethala et al., 2007; Seethala, 2013; WHO Classification of Tumours Editorial Board. Head and Neck Tumours, 2024). EMC is the prototypical 'biphasic' salivary gland tumour composed of a tubular to nested bilayered arrangement of inner (luminal) ductal cells and outer (abluminal) myoepithelial cells. EMC invades in a deceptively innocuous fashion with a multinodular pushing border rather than frankly infiltrative (Fig. 6A). About 25-30% of cases show at least partial encapsulation (Seethala et al., 2007). OEMC is a rare subtype of EMC. Oncocytic changes may be seen focally in many otherwise conventional EMCs. However, OEMC is generally only designated as subtypes when the oncocytic components comprise greater than 50% of the tumour area (Fig. 6A) (Seethala

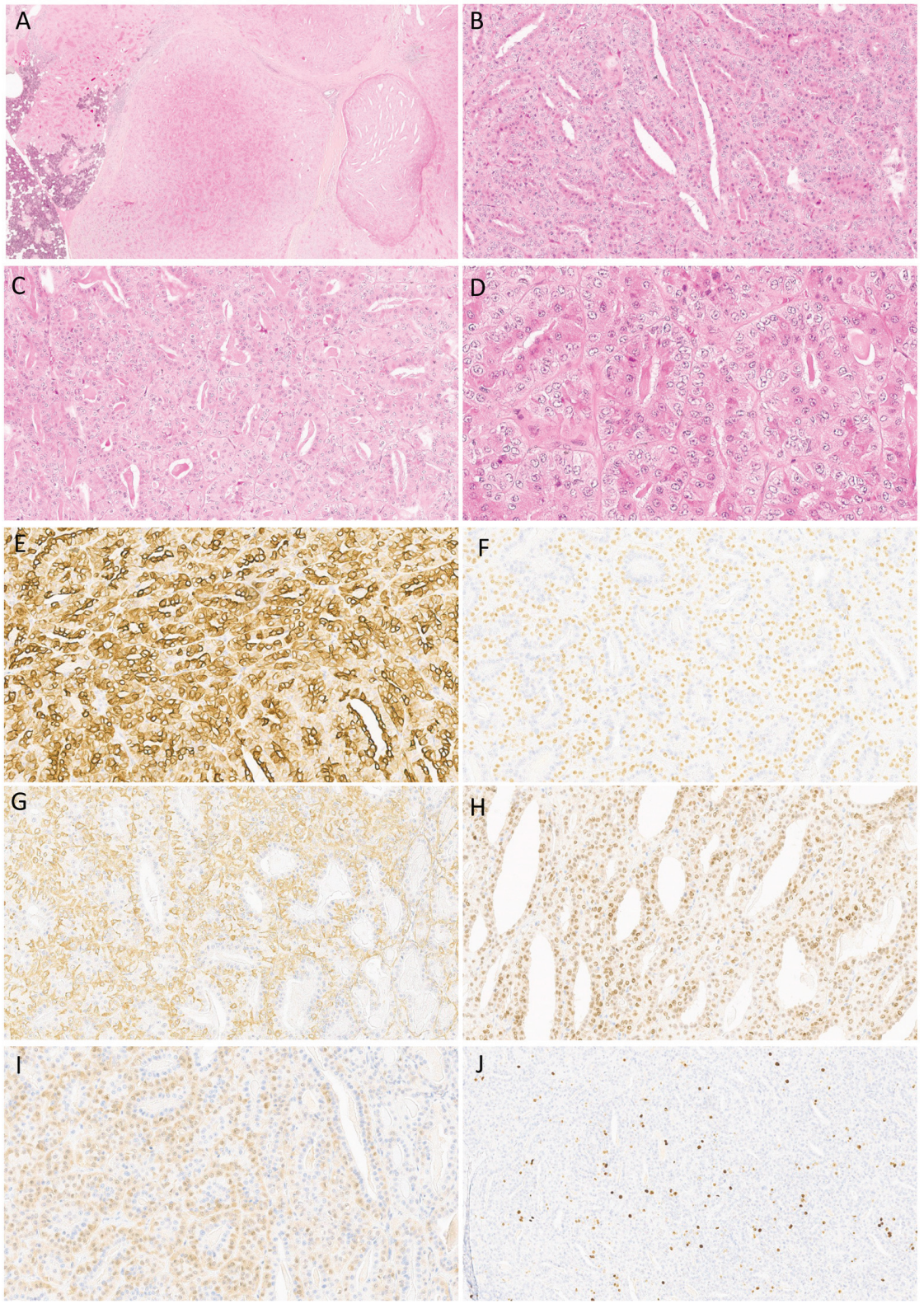

Fig. 6. Example of OEMC. Tumour proliferation displays a pushing infiltrative pattern **(A)**. The OEMC consists of a bilayer arrangement of tubules with inner ductal cells and abluminal myoepithelial cells **(B)**, where the larger calibre tubules are more akin to striated than intercalated ducts **(C)**. The ductal component consists of cuboidal to columnar oncocytic cells with granular cytoplasm, while the outer myoepithelial cell layer varies and ranges from clear to oncocytic **(D)**. The immunohistochemical profile is diffusely positive for CK7 **(E)**, p63 **(F)**, smooth muscle actin **(G)**, SOX10 **(H)**, and S100 **(I)**. The KI67 proliferation index is low **(J)**. A, x 10; B, C, E-J, x 20; D, x 40.

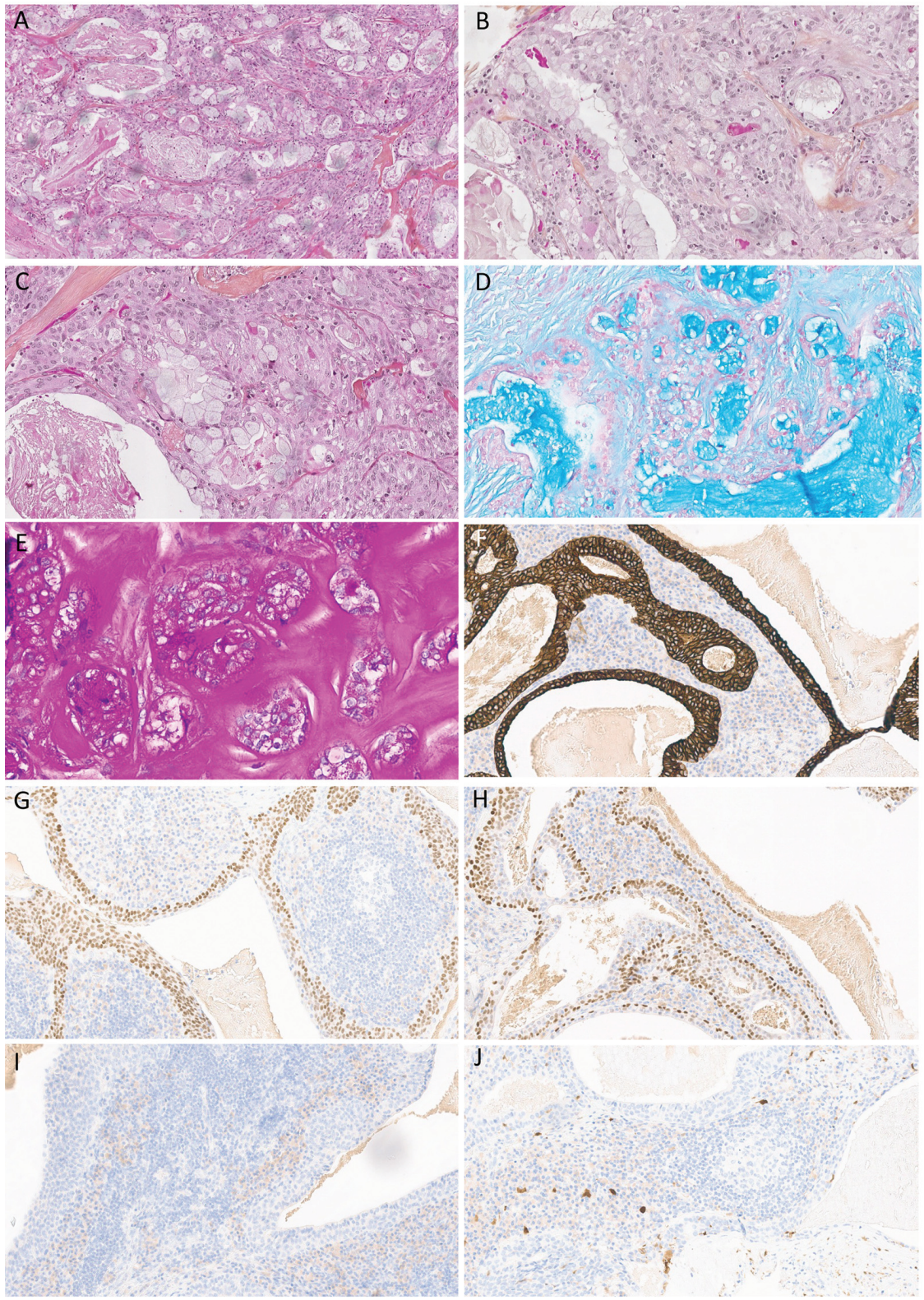

Fig. 7. Example of OMEC. Tumour proliferation is composed exclusively of oncocytic cells **(A)**, which are arranged in sheets associated with mucus-secreting cells **(B)**. The oncocytes with abundant granular eosinophilic cytoplasm alongside central nucleolated nuclei with clusters of mucus-secreting cells **(C)**. The mucocytes with intracytoplasmic mucin vacuoles demonstrated positivity with special stains: Alcian Blue **(D)** and Periodic Acid-Schiff **(E)**. The immunohistochemical profile is diffusely positive for CK7 **(F)**, positive in the peripheral tumour for p63 **(G)** and p40 **(H)**; and negative for SOX10 **(I)** and S100 **(J)**. A, x 10; B, C, F-J, x 20; D, E, x 40.

et al., 2007; Seethala, 2013). OEMC is unique in that they are "pink" or oncocytic in appearance, challenging the classical requirement for clear cell morphology in the myoepithelial component of EMC. It consists of a bilayer arrangement of tubules with inner ductal cells and abluminal myoepithelial cells. However, the tubules are larger in calibre, more akin to striated than intercalated ducts (Fig. 6B,C). The ductal component in OEMC consists of cuboidal to columnar oncocytic cells with granular cytoplasm (Fig. 6D). The outer myoepithelial cell layer varies and ranges from clear to oncocytic. Nuclei of the myoepithelial component are larger and more vesicular than the ductal component. The biphasic appearance of OEMC resembles that of classical EMC. The luminal ductal components strongly express CK7 (Fig. 6E), as detected using pankeratin cocktails or low-molecular-weight keratins. Myoepithelial cells are positive for p63 (Fig. 6F) and muscle markers, including smooth muscle actin (Fig. 6G), calponin, and vimentin. While cytokeratin staining also highlights the myoepithelial cell layer, the intensity is lower compared to that of the ductal component. The SOX10, S100, and traditional myoepithelial markers in EMC exhibit variable staining (Fig. 6H,I). Occasionally, GFAP stains the myoepithelial component, and Ki67 typically shows less than 20% proliferation (Fig 6J). Strong p53 immunoreactivity is rare (Seethala et al., 2007). Immunostaining for RAS Q61R (SP174) has been described in approximately 70% of EMC, and immunostaining is confined to the cytoplasm of myoepithelial cells (Nakaguro et al., 2021). EMC is characterised by *HRAS* exon 3 hotspot mutations in up to 85% of de novo cases. The most frequent mutations are *HRAS* Q61R, followed by *HRAS* Q61K and *HRAS* G13R. *HRAS* mutations are specific to EMC and have not been observed in histological mimics such as PA, adenoid cystic carcinoma, basal cell adenoma, or basal cell adenocarcinoma. Notably, *HRAS* mutations are often absent in EMC arising in PA (De Cecio et al., 2017; Felisiak-Gołąbek et al., 2018). Co-mutations involving *PIK3CA*, *AKT1*, and *ARID1A* have been described in EMC (El Hallani et al., 2018), while high-grade transformation can exhibit *TP53*, *FBX7*, or *SMARCB1* mutations (Urano et al., 2019). Other genetic changes in EMC arising in a background of PA can show *PLAG1* or *HMGA2* alterations. The 5- and 10-year survival for EMC has been reported as 94% and 82%, respectively, with only a 2% rate of distant metastasis, likely secondary to improved initial surgical management (Seethala, 2013).

Other complex patterns

Oncocytic mucoepidermoid carcinoma (OMEC)

MEC is composed of mucinous, intermediate, clear, and squamous neoplastic cells arranged in cystic and solid growth patterns in variable proportions (WHO Classification of Tumours Editorial Board. Head and Neck Tumours, 2024). MEC is the most common salivary gland malignancy (Boukheris et al., 2009; WHO Classification of Tumours Editorial Board. Head and Neck Tumours, 2024). MEC occurs across a wide age range, from childhood to old age, with an average age in the 5th decade of life. It shows a slight female predominance, with a male-to-female ratio from 1:1.1 to 1:1.5 (Dombrowski et al., 2019). Approximately half of MECs are found in major salivary glands, commonly in the parotid gland, followed by the submandibular and sublingual glands. In minor salivary glands, the palate is the most frequent site, followed by the buccal mucosa (Dombrowski et al., 2019; Dahan et al., 2021). OMEC is a rare and diagnostically challenging subtype (Weinreb et al., 2009). OMEC is characterised predominantly by oncocytic cells and has been defined by an arbitrary cut-off of 75% of oncocytic cells (Fig. 7A). The fundamental importance of recognising OMEC is in distinguishing it from its mimics (Skálová et al., 2020a). The most challenging differential diagnosis involves distinguishing OMEC from benign oncocytoma or low-grade oncocytic tumours of indeterminate malignant potential, as well as from cellular PAs and/or myoepitheliomas with marked oncocytic metaplasia due to the lack of mucocytes (Alsugair et al., 2024a,b). Although the presence of mucocytes alone is not sufficient to confirm a diagnosis of MEC. (Figs. 7B and 7C) (Michal et al., 1998; Skálová et al., 1999; Bezić and Glavina-Durdov, 2011; Liao et al., 2016; Alsugair et al., 2024a,b). In challenging cases, mucocytes with intracytoplasmic mucin vacuoles can be identified using special stains such as Alcian Blue (Fig. 7D) or Periodic Acid-Schiff (PAS, Fig. 7E). In OMEC, PLAG1 is consistently negative, while CK7-positive epithelial cells are a characteristic finding (Fig. 7F) (Alexiev et al., 2017). Although diffuse positivity for p63 (Fig. 7G) and p40 (Fig. 7H) has been observed (Weinreb et al., 2009), these markers are not specific and have been reported in some cases at the periphery of the tumour (Vial et al., 2024). Generally, SOX10 (Fig. 7I) and S100 (Fig. 7J) are negative, which helps to distinguish OMEC from ductal cell-derived salivary neoplasms, such as ACC and SC (Ohtomo et al., 2013). However, SOX10 positivity has occasionally been reported in MECs (Hsieh et al., 2016). MECs are known to harbour characteristic gene fusions, such as *CRTC1::MAML2* or *CRTC3::MAML2*, in up to 80% of cases (Skálová et al., 2020a). The identification of these fusions serves as a valuable diagnostic tool, particularly in challenging cases (García et al., 2011; Bishop et al., 2018) However, their absence does not completely rule out the diagnosis of MEC. In such situations, recent advances in transcriptomic and DNA methylation analyses have proven helpful, revealing distinct molecular profiles. Unfortunately, these technologies are currently limited to major medical centres (Jurmeister et al., 2024; Vial et al., 2024). Several histopathologic grading systems for MEC have been developed to improve prognostics and guide treatment decisions. These include the AFIP (Goode et al., 1998), Brandwein (Brandwein et al., 2001), and MSK systems (Katabi et al., 2014). However, none of

these grading systems have been validated for OMEC. For instance, the cystic component, an important parameter in these grading systems, is not applicable to OMEC, as the vast majority of OMEC cases have a cystic component of less than 25%. Despite this, OMEC often exhibits low levels of atypia. In terms of prognosis, the five-year overall survival rates for MEC (including OMEC) are stratified by grade: approximately 90% for low-grade MEC, 86% for intermediate-grade, and 55% for high-grade (Taylor et al., 2020; Dahan et al., 2021).

Oncocytic adenocarcinoma not otherwise specified (OANOS)

The discovery of new morphogenetic types of salivary gland adenocarcinoma (Nikitakis et al., 2004; Mills et al., 2016) has significantly refined the classification of these tumours. As a result, adenocarcinoma not otherwise specified (ANOS) now accounts for only 5-10% of salivary gland carcinomas. ANOS typically presents as a rapidly growing mass, often arising in the context of a preexisting or recurrent PA. It predominantly affects older adults, with peak incidence observed in the 6th to 7th decades of life. The diagnosis of ANOS is established only after excluding other primary salivary gland carcinomas, such as SDC, MEC, polymorphous adenocarcinoma, and high-grade transformations of other salivary carcinoma types. Historically, oncocytic carcinoma was classified as a carcinoma predominantly composed of oncocytes. However, oncocytic features are now recognised across various salivary gland tumours, challenging its designation as a distinct pathological entity. Recent molecular studies have revealed that many tumours previously classified as OANOS are, in fact, OSDC, or OMEC (Simpson, 2013; Skálová et al., 2020a; WHO Classification of Tumours Editorial Board. Head and Neck Tumours, 2024). Consequently, the latest WHO classification no longer recognises oncocytic carcinoma as an independent category but instead classifies it under emerging entities (WHO Classification of Tumours Editorial Board. Head and Neck Tumours, 2024). Our group recently reported that all cases initially diagnosed as OANOS were reclassified as either OSDC or OMEC based on morphology, immunohistochemistry, and/or molecular biology. This finding strongly supports the notion that OANOS is not a distinct pathological entity. However, it remains essential to retain the oncocytic subtype within the ANOS category, because transcriptomic analyses, key for precise reclassification, are not widely accessible to all pathologists. Therefore, OANOS should be considered a provisional diagnosis until advanced molecular tools allow for accurate classification (Vial et al., 2024).

Conclusion

Oncocytic carcinomas of the salivary glands represent a diverse and diagnostically challenging group of malignancies with overlapping histopathologic and immunohistochemical characteristics. The classification of these tumours into monophasic, biphasic, and complex morphological patterns highlights their heterogeneity and the necessity for integrative diagnostic approaches. Monophasic patterns, including oncocytic intraductal carcinoma (OIDC), oncocytic salivary ductal carcinoma (OSDC), acinic cell carcinoma (ACC), and secretory carcinoma (SC), demonstrate distinct histopathological and immunohistochemical profiles that facilitate their identification. Similarly, biphasic tumours, such as oncocytic epithelial-myoepithelial carcinoma (OEMC) and oncocytic adenocarcinoma not otherwise specified (OANOS), further complicate classification due to their dual cellular composition. Moreover, complex-patterned tumours, such as oncocytic mucoepidermoid carcinoma (OMEC), add another layer of diagnostic complexity, necessitating molecular profiling for precise classification. The accurate diagnosis and classification of oncocytic carcinomas of the salivary glands require a multidisciplinary approach that integrates histopathological assessment, immunohistochemistry, and molecular analysis. Further research into the molecular underpinnings of these tumours will not only refine classification systems but also improve prognostics and pave the way for personalised treatment strategies, ultimately enhancing patient outcomes.

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