Educational Case

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Educational Case: Diagnostic Approach to Salivary Gland Neoplasms

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.[1]

Keywords
pathology competencies, organ system pathology, head and neck neoplasia, salivary gland tumors, salivary duct carcinoma, cytopathology, genetic basis of salivary gland neoplasia

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Primary Pathology Learning Objective

Objective HN2.1: Benign and Mucoepidermoid Tumors of Salivary Glands. Distinguish the clinicopathologic features of the 2 benign tumors (pleomorphic adenoma or mixed tumor and Warthin tumor) from the malignant mucoepidermoid carcinoma.

Competency 2: Organ System Pathology, Topic: Head and Neck (HN), Learning Goal 2: Head and Neck Neoplasia

Secondary Pathology Learning Objectives

Objective CYP1.2: Categorizing Diagnostic Certainty. Compare and contrast the degree of diagnostic certainty applied to general diagnostic categorization in cytologic diagnosis.

Competency 3: Diagnostic Medicine and Therapeutic Pathology, Topic: Cytopathology (CYP); Learning Goal 1: Cytologic Diagnosis

Objective GE3.3: Molecular Testing in Oncology. Explain the application of molecular testing for diagnosis, prognostication, and therapeutic follow-up of oncologic diseases.

Competency 3: Diagnostic Medicine and Therapeutic Pathology, Topic: Genomics (GE); Learning Goal 3: Genetic Basis of Neoplasia

Patient Presentation

A 62-year-old man presents to emergency department with a progressive right facial swelling for the past year. In addition, he noticed mild right mandibular pain and right face numbness for the past year. He does not have weight loss, loss of appetite, fever, or shortness of breath. The patient has a past surgical history of a broken jaw that was treated 5 years ago. He has a 76 pack-year smoking history. There is no family history of cancer.

Diagnostic Findings, Part 1

The patient's vital signs are stable. Head and neck physical examination reveals a large mass along the entire right ramus that was firm to palpation but not tender or painful and had no

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overlying erythema. The mass is associated with other findings on the right side of the face including: swelling, facial nerve paralysis, trismus (reduced jaw opening), and mild periorbital swelling. No intraoral swelling or tenderness are noticed.

Questions and Discussion Points, Part 1

Based on the Clinical Presentation, What Is the Most Likely Differential for This Patient?

Although evaluating unilateral facial swelling, it is very crucial to focus on the duration of the symptoms to differentiate acute versus chronic conditions which will be helpful for further diagnostic evaluation. Facial swelling can be classified into different groups including acute swelling usually due to inflammatory process, nonprogressive swelling, and slowly or rapidly progressive swelling.[2] Acute swelling is seen in acute inflammation of the salivary glands "sialadenitis." It can also happen in post radiation sialadenitis, reactive lymph node inflammation "lymphadenitis," dental infections, and abscesses. Nonprogressive swelling is suggestive of a congenital anomaly, whereas slowly progressive swelling is seen in benign tumors, vascular malformations, benign vascular tumors (eg, hemangioma), and fibrous dysplasia. Rapidly progressive swellings are usually associated with malignancies.[2,3]

Acute sialadenitis is inflammation of salivary glands due to bacterial or fungal infection, or secondary to obstruction by salivary gland stones (sialolithiasis). Acute lymphadenitis is an inflammation of the lymph nodes usually due to bacterial or fungal infections too. Post treatment sialadenitis occurs after radiotherapy, radioactive iodine, or surgery. Additionally, an abscess is a painful collection of pus, usually caused by a bacterial infection. These conditions are usually associated with fever and pain/tenderness over the swelling area.[3] Clinically, our patient had only mild pain and was afebrile. Also, his history indicated a progressing swelling for the past 1 year. Abscess and other non-neoplastic "infectious/inflammatory" conditions have sudden onset of swelling associated with pain, fever and with an induration, and tenderness over the swollen area on physical examination. Thus, these conditions can be ruled out in our patient.

Our patient's history of painless progressive swelling over the past 1 year is more likely due to a neoplastic process. Benign neoplasms are usually very slow-growing, well-circumscribed with no tissue destructive invasion, while malignant neoplasms are usually associated with destructive tissue invasion and distant metastasis. In this case, the mass was growing to reach a large size relatively fast (1 year) with associated facial symptoms indicating tissue destructive invasion such as facial swelling, facial nerve paralysis, trismus, and mild periorbital swelling. So, clinically our patient's presentation is worrisome for a malignant neoplastic process.

The differential diagnosis for a neoplastic process in the cheek area will include non salivary glands and salivary gland tumors. Non salivary gland malignant tumors will include malignant skin tumors such as squamous cell carcinoma, basal cell carcinoma, or sebaceous carcinoma. Malignant salivary gland tumors are included in the differential diagnosis too. Metastatic malignant tumors to the salivary glands or neck lymph nodes should be included as well as salivary gland lymphomas. Our patient did not have any history of other primary tumors so metastatic tumors are low in the differential diagnosis. Also, lymphoma is usually associated with systemic signs such as weight loss, night sweats, fatigue, and fever. Our patient did not have any of these symptoms. Thus, lymphoma should also be placed low on the differential diagnosis list.

What Diagnostic Testing Is Available for This Patient?

The clinical history and physical examination findings suggest a neoplasm (favoring malignant over benign) computed tomography (CT) scan or magnetic resonance imaging can help in evaluating the nature and location of the lesion, the extent of disease locally and presence of lymph node metastasis.

Diagnostic Findings, Part 2

Computed Tomography

The patient had a CT of facial bone with contrast which reported a 9-cm infiltrative right parotid gland mass with perineural involvement, and erosion of the right greater wing of sphenoid, expansion of the foramen ovale with intracranial extension causing mild mass effect on the right temporal lobe. There is erosion of the right carotid canal and of the inferior mastoid air cells and right sigmoid plate. The lesion demonstrated scattered level 1 and right level 2 lymph nodes, which may represent metastatic disease.

The patient also had a CT scan of chest showing multiple bilateral pulmonary nodules highly suspicious for metastases from the identified parotid tumor.

Questions and Discussion Points, Part 2

How Useful was the CT Scan in Differentiating Benign Versus Malignant Salivary Gland Tumors?

In our case, CT imaging identified invasion to adjacent anatomic structures as well as the findings of lymphadenopathy and pulmonary nodules which suggest that the lesion is an aggressive malignant neoplasm arising from the parotid gland even prior to obtaining a tissue diagnosis.

What is the Preferred Modality to Obtain a Tissue Diagnosis for This Lesion?

Fine needle aspiration (FNA) is the preferred method for primary diagnosis/triaging of salivary gland lesions as it is associated with less risk of infection and surgical planes contamination compared to incisional biopsy. Ultrasound guidance can be utilized during FNA to improve sampling accuracy. Also, during FNA collection of extra material for cell blocks (formalin-fixed tissue preparation) which is of crucial

importance for salivary gland lesions because ancillary studies (immunocytochemistry and molecular/cytogenetics studies) can be performed on cell blocks and aid in differentiating salivary gland tumors.

Fine needle aspiration biopsy was performed in this case and revealed clusters, sheets, and cribriform groups of overtly malignant polygonal cells with hyperchromatic eccentric nuclei and prominent nucleoli. The cells demonstrated abundant granular and vacuolated cytoplasm. Single malignant cells and abnormal mitotic figures were noted, and necrosis was also present in the background. These features were suggestive of a malignant neoplasm of an epithelial origin which can be proven by immunocytochemistry.

Diagnostic Findings, Part 3

A battery of immunocytochemistry stains was done on the cell block, and the tumor was positive for cytokeratin, androgen receptor (AR), and HER2.

Given, the clinical features along with imaging and FNA findings, a diagnosis of high-grade carcinoma consistent with salivary duct carcinoma (SDC) arising from the right parotid gland was rendered and a surgical resection was carried out.

Questions and Discussion Points, Part 3

Discuss the Histomorphologic Features of the Resection Specimen

A surgical resection of the parotid gland (parotidectomy) was performed along with a right neck lymph nodes dissection. Histological examination of the parotid gland tumor showed invasive malignant tumor with different growth patterns including cell nests with cribriforming, solid and cystic areas. The tumor cells were large, cuboidal to polygonal with round often centrally situated hyperchromatic nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm (Figure 1A and B). Features similar to breast ductal carcinoma in situ with roman bridges pattern (bands of neoplastic epithelium arched over luminal spaces) and central comedo-type necrosis were seen. Perineural invasion and lymphovascular invasion and invasion into adjacent salivary glands and surrounding soft tissue was also identified (Figure 1C-E). Multiple neck lymph nodes were positive for metastatic carcinoma.

As with the FNA biopsy, the tumor cells were positive for cytokeratin's, AR (Figure 1F), HER2, and GATA-3, and negative for p63. The final diagnosis was SDC arising from the parotid gland with multiple right neck lymph nodes metastasis.

What Kind of Tumors can Arise From the Salivary Glands?

In order to answer this question, we need to understand the normal histology of the salivary gland tissue and its different cell constituents.

Salivary gland is composed of mucous and serous acini. Mucous acinar cells are elongated structures with peripheral nuclei at the basal region due to high mucous production within the cytoplasm. In contrast, serous acini are triangular-shaped cells with round nuclei responsible for more aqueous secretion. The ductal network can be observed where the proximal intercalated ducts consisting of single cuboidal epithelial layer are directly connected to the secretory units. Intercalated ducts are followed by striated ducts which perform most of the ion exchange between salivary fluid and extracellular matrix through several membrane folding (striations) on their basal side. Finally, excretory duct is a calibrated and stratified epithelial collecting duct responsible for carrying the final secretions to the oral cavity. Myoepithelial cells surround acini and intercalated ducts and mediate contraction to expel the salivary content to the ductal network. Myoepithelial cells are flattened and elongated cells with long/irregular nuclei and connected via desmosomes to acinar and ductal cells[4] (Figure 2). Benign and malignant tumors can arise from any of the cells described above and will have a distinct morphology and immunohistochemical profile (Figure 3). Benign tumors of the salivary gland are more common than their malignant counterparts.

Benign tumors are usually well circumscribed with no local tissue invasion. Pleomorphic adenoma (PA) and Warthin tumor are the most common benign salivary gland tumors accounting for 94% of all salivary gland tumors.[5] Pleomorphic adenoma is also known as benign mixed tumors due to dual origin from epithelial and myoepithelial elements and comprise of 70% to 80% of benign salivary gland tumors (Figure 3A-B). The second most common tumor, which occurs almost exclusively in parotid gland, is Warthin tumor comprising 25% to 32% of all benign tumors. The "doughy" texture of the mass is a frequent finding. They are sometimes multifocal (10%) and bilateral (15%). This clinical presentation of benign tumors keeps them at higher end of differentials and needs further evaluation (Figure 3C-D).

On the other hand, malignant neoplasms are usually locally aggressive with destructive tissue invasion and can also present with metastasis to lymph nodes or distant metastasis. In our case, the patient presents with a mass associated with facial nerve paralysis and right periorbital swelling which are features of local tissue destructive invasion and are indicative of a malignant tumor. Malignant salivary gland neoplasms account for 6% of all head and neck tumors and <0.5% of all cancers diagnosed annually in United States. A ratio of 40:10:1 is cited for malignant tumors of parotid, submandibular, and sublingual glands, respectively.[6]

Mucoepidermoid carcinoma (MEC) is the most common malignant salivary gland neoplasm in both adult and children consisting of 35% of all malignant salivary gland tumors. Presenting symptoms include rapid growth, pain, immobility, facial asymmetry, skin changes, lymphadenopathy, and nerve dysfunction. The patient reported most of these symptoms (facial asymmetry, lymphadenopathy, and cranial nerve dysfunction), making this diagnosis high on differential diagnosis list.

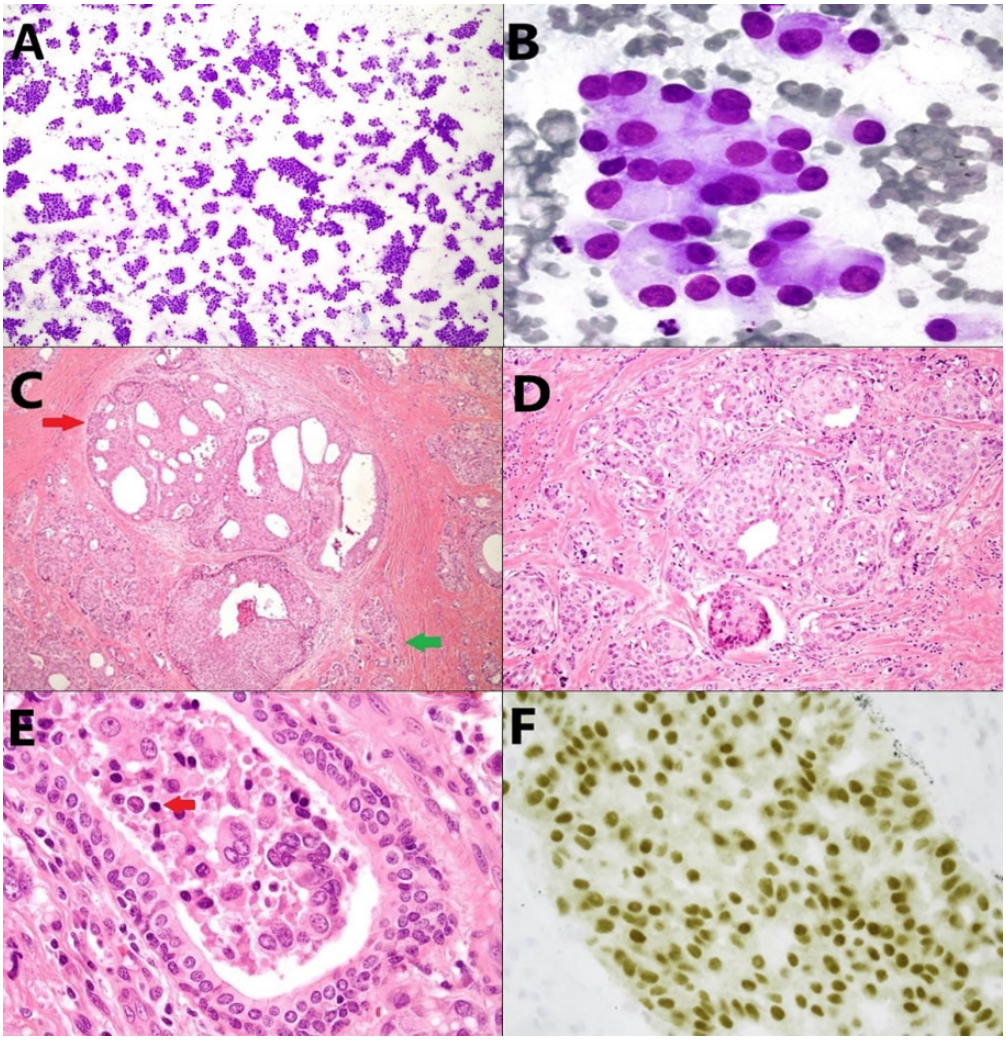

Figure 1. (A-F) Cyto/histomorphology of salivary duct carcinoma. (A) Cellular smear with many clusters of malignant cells (Romanowsky stain, ×100). (B) Groups of malignant cells with large, round to oval eccentric nuclei, prominent nucleoli and hyperchromatism are noted. The cytoplasm is granular to dense (Romanowsky stain, ×400). (C) Invasive salivary duct carcinoma, with cribriform pattern (red arrow), infiltrating malignant glands and marked stromal desmoplastic reaction (green arrow; H&E, ×100). (D) Invasive salivary duct carcinoma, cancers cells are plumped with eosinophilic granular cytoplasm (H&E, ×200). (E) Malignant duct filled with a mixture of necrotic tumor cells with pyknotic dark nuclei (red arrow) and viable tumor cells (H&E, ×400). (F) Strong androgen receptor (AR) positivity in salivary duct carcinoma (H&E, ×400).

Adenoid cystic carcinoma (ACC) is second most common salivary gland tumor which constitutes about 22% of all malignant salivary gland tumors. Adenoid cystic carcinoma is a slow-growing, painful aggressive neoplasm with notable capacity for perineural spread.[7] Acinic cell carcinoma is another common salivary gland malignancy comprising 15% of malignant salivary gland tumors.

Carcinoma ex pleomorphic adenoma (CXPA) is a malignant transformation either from a primary (de novo) or recurrent benign PA. It is a rare, aggressive neoplasm forming 5% to 25% of malignant slavery gland tumors and occur mainly in the major salivary glands.[8]

Salivary duct carcinoma "the tumor presented in our case" is a high-grade salivary gland tumor first described by Kleinsasser and Klein[9] and represents 1% to 3% of all malignant salivary gland tumors. It arises from the ductal epithelium of the salivary gland tissue and histologically it resembles high-grade breast ductal carcinoma.[10] It most commonly occurs in the parotid gland and has male predominance.[10,11] Most cases of SDC develop de novo but some may arise from preexisting PA (CXPA).[12] Clinically, SDC presents as a firm, painful, rapidly growing mass with facial paralysis and a tendency to metastasize through the temporal bone via perineural extension.[13,14] Sixty percent of patients with this tumor die within 5 years of initial diagnosis and despite surgery and adjuvant chemoradiotherapy >33% have local recurrence and >50% of patients will develop metastases to the brain, bone, liver, lungs, and skin.

Invasive ductal carcinoma (IDC) of the breast is morphologically similar to SDC. When patients, especially females, presents

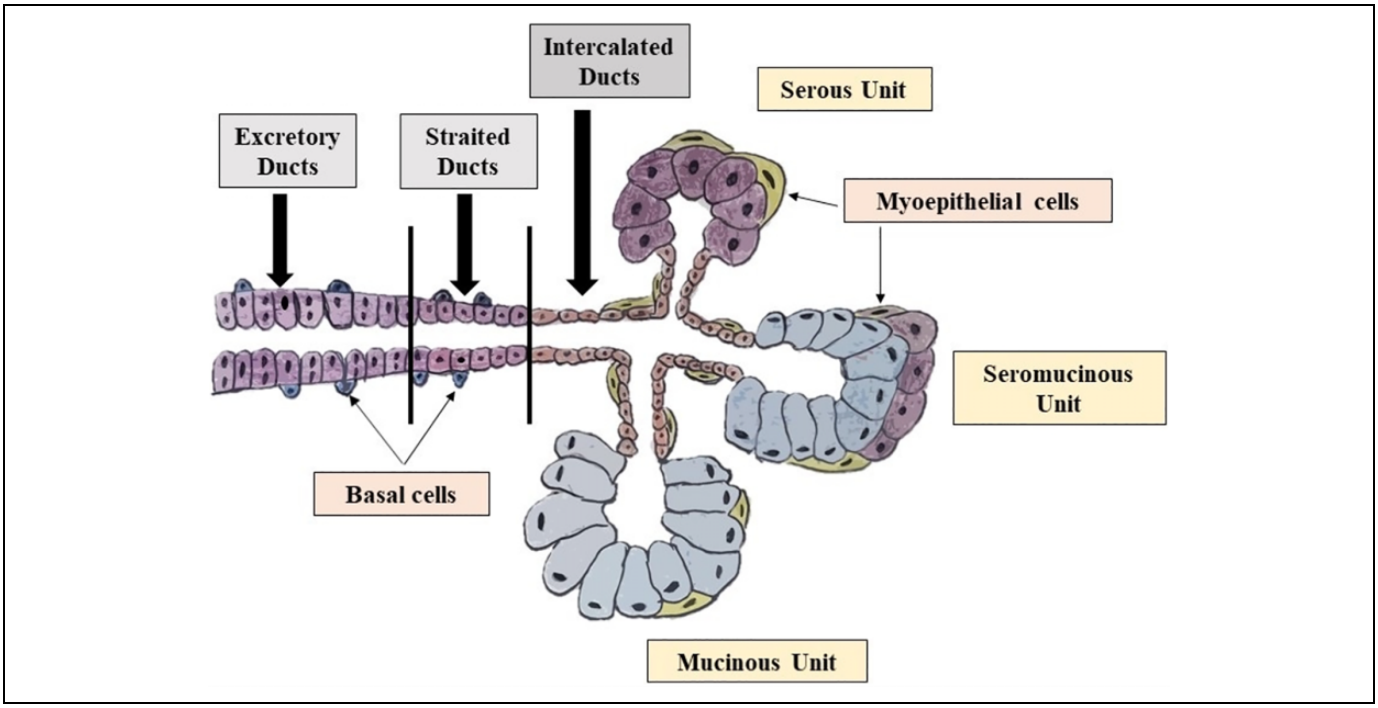

Figure 2. Sketch illustrating normal salivary gland histology.

with metastatic disease, then both SDC and IDC of breast are high on differentials diagnosis. However, immunohistochemistry (IHC) can be helpful as breast tumors are more likely to be Estrogen receptor(ER) and Progesterone receptor(PR) positive. Also, SDC usually shows strong positive expression of AR which is helpful in differentiating the 2 neoplasms.[15]

The strong AR receptor expression in SDC is immunophenotypically similar to prostate adenocarcinoma. Hence, when a male patient with AR+/PSA+/PAP+ presents with adenocarcinoma of prostate with unknown primary then SDC should be considered as well. SDC is a highly aggressive tumor with distant metastasis occurring commonly.[16]

How Can Ancillary Tests Analysis Help in Differentiating SDC From Other High-Grade Salivary Gland Tumors?

The majority of SDCs (74%) have alterations in either the mitogen-activated protein kinase (MAPK) MAPK pathway (BRAF, HRAS, and NF1) or in ERBB2, indicating that MAPK pathway activation and ERBB2 amplification are the major oncogenic drivers in SDCs.[17]

The differential diagnosis of SDC includes high-grade MEC with about two-thirds of MEC cases show a *t* (11;19) (q21; p13) chromosomal translocation with *CRTC1-MAML2* gene fusion. Another differential is ACC which morphologically looks distinct and harbor a distinct translocation *t* (6;9) (q22-23; p23-24) resulting in *MYB-NFIB* gene fusion. Acinic cell carcinoma is a low-grade malignant salivary gland tumor that can undergo high-grade transformation, but IHC will differentiate it from SDC as it is positive for DOG-1 and SOX10 which is negative in SDC. Metastatic breast or prostatic carcinoma show overlapping histologic and immunohistochemical features but rarity of breast or prostate cancer metastasizing to salivary glands essentially and negative clinical history of primary tumor in the breast or prostate exclude the diagnosis.[17,18]

What is the Treatment Approach for a Patient with Salivary Ductal Carcinoma?

There are no specific treatment guidelines for SDC but surgery is the mainstay. Many authors recommend total parotidectomy in cases with local invasion or even T1 tumors due to high chance of local recurrence which is often life threatening. If facial nerve paralysis is present then radical parotidectomy is mandatory.[19]

Adjuvant radiation therapy is indicated in cases of extra parotid extension, positive resection margins, cervical lymph node metastasis, and/or neurologic invasion. Chemotherapy is generally reserved for metastatic disease.[20] Like other salivary gland tumors, SDC shows poor response to classical chemotherapy. Therefore, new targeted therapy considering the overexpression of HER2 and AR in SDC have been proven beneficial in these patients.[21,22]

Teaching Points

- Mass in the cheek can be caused by a variety of disease process, neoplastic and non-neoplastic.
- Clinical presentation along with imaging modalities can give a general good idea about disease nature.
- Fine needle aspiration is the preferred modality to obtain a tissue diagnosis for salivary gland lesions and guides

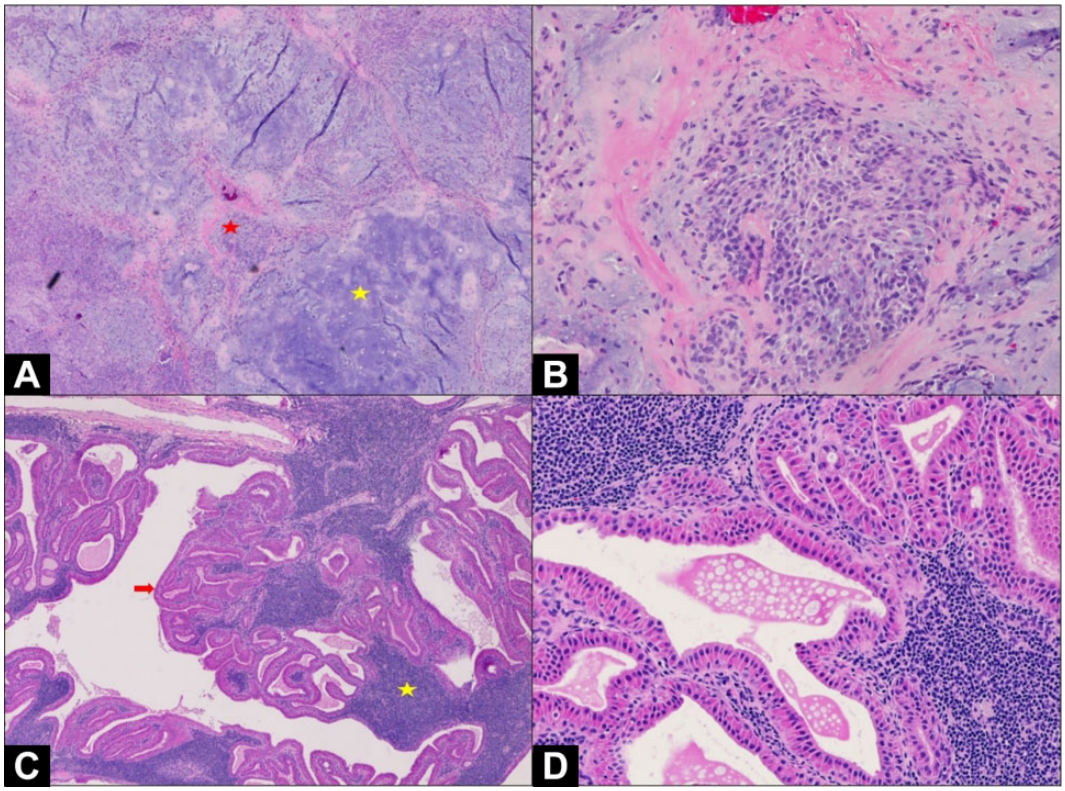

Figure 3. A, Pleomorphic adenoma (mixed tumor) composed of mixed components of chondromyxoid matrix with variable cellularity "yellow star" and epithelial/myoepithelial proliferations "red star" (20X, H&E). B, myoepithelial cells of pleomorphic adenoma may appear in clusters "center" or dispersed and can be spindly or plasmacytoid (200X, H&E). C, Warthin tumor composed of 2population of cells, oncocytic epithelium "red arrow" and lymphoid population "yellow star" (20X, H&E). D, Double layered oncocytic cells are columnar with some nuclei oriented toward the lumen while other nuclei oriented toward the basal surface. Also notice the luminal secretions (the tumor is usually cystic) and stromal lymphoid population (200X, H&E).

clinical management by triaging salivary gland lesions into non-neoplastic or neoplastic (benign or malignant) with high degree of certainty if good amount of diagnostic material is collected.

- Up to 80% of salivary gland tumors appear in parotid gland and is the most common gland to be affected with malignant neoplasms.
- Benign tumors such as PA and Warthin tumor account for 94% of salivary gland neoplasm and malignant tumors account for the remaining 6%.
- Most common benign salivary gland tumor is PA and accounts for 70% to 80% of benign salivary gland tumors, whereas most common malignant salivary gland tumor is MEC and accounts for 35% of malignant salivary gland tumors.
- In general, the histologic features of each salivary gland tumor are distinct and diagnostic; however, there is some degree of morphologic overlap among different tumors.
- Salivary duct carcinoma (SDC) is a high-grade salivary gland tumor and represents 1% to 3% of all malignant salivary gland tumors. Histologically, it resembles the high-grade breast ductal carcinoma.
- The differential diagnosis of SDC includes high-grade, MEC, ACC, acinic cell carcinoma, metastatic breast ductal carcinoma, and prostate carcinoma.
- Immunohistochemical stains and molecular/cytogenetic studies can be very useful in differentiating between tumors leading to the correct diagnosis.
- The majority of SDCs (74%) have alterations in either the MAPK pathway (BRAF, HRAS, and NF1) or in ERBB2, indicating that MAPK pathway activation and ERBB2 amplification are the major oncogenic drivers in SDCs.

Declaration of Conflicting Interests

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References

1. Knollmann-Ritschel BEC, Regula DP, Borowitz MJ, Conran R, Prystowsky MB. Pathology competencies for medical education and educational cases. *Acad Pathol*. 2017;4. doi:10.1177/2374289517715040
2. Thomas AE, Kurup S, Jose R, Soman C. Facial swelling as a primary manifestation of multiple myeloma. *Case Rep Dent*. 2015;2015:319231. doi:10.1155/2015/319231
3. Ugga L, Ravanelli M, Pallottino AA, Farina D, Maroldi R. Diagnostic work-up in obstructive and inflammatory salivary gland disorders. *Acta Otorhinolaryngol Ital*. 2017;37(2):83-93. Work-up diagnostico nella patologia ostruttiva e infiammatoria delle ghiandole salivari. doi:10.14639/0392-100x-1597
4. de Paula F, Teshima THN, Hsieh R, Souza MM, Nico MMS, Lourenco SV. Overview of human salivary glands: highlights of morphology and developing processes. *Anat Rec*. 2017;300(7):1180-1188. doi:10.1002/ar.23569
5. Zhan KY, Khaja SF, Flack AB, Day TA. Benign parotid tumors. *Otolaryngol Clin North Am*. 2016;49(2):327-342. doi:10.1016/j.otc.2015.10.005
6. Adriane P, Concus M, Theresa N, Tran M. Malignant diseases of the salivary glands. In: Lalwani AK, ed. *Current Diagnosis & Treatment in Otolaryngology: Head & Neck Surgery*. 3rd ed. McGraw Hill Medical; 2012:chap 19.
7. Godge P, Sharma S, Yadav M. Adenoid cystic carcinoma of the parotid gland. *Contemp Clin Dent*. 2012;3(2):223-226. doi:10.4103/0976-237X.96838
8. Antony J, Gopalan V, Smith RA, Lam AKY. Carcinoma ex pleomorphic adenoma: a comprehensive review of clinical, pathological and molecular data. *Head Neck Pathol*. 2012;6(1):1-9. doi:10.1007/s12105-011-0281-z
9. Kleinsasser O, Klein HJ. Basal cell adenoma of the salivary glands [in German]. *Arch Klin Exp Ohren Nasen Kehlkopfheilkd*. 1967;189(3):302-316. Basalzelladenome der Speicheldrusen.
10. Seethala RR, Stenman G. Update from the 4th edition of the world health organization classification of head and neck tumours: tumors of the salivary gland. *Head Neck Pathol*. 2017;11(1):55-67. doi:10.1007/s12105-017-0795-0
11. Gal R, Strauss M, Zohar Y, Kessler E. Salivary duct carcinoma of the parotid gland. Cytologic and histopathologic study. *Acta Cytol*. 1985;29(3):454-456.
12. Simpson RHW. Salivary duct carcinoma: new developments—morphological variants including pure in situ high grade lesions; proposed molecular classification. *Head Neck Pathol*. 2013;7(suppl 1):S48-S58. doi:10.1007/s12105-013-0456-x
13. Nguyen BD, Roarke MC. Salivary duct carcinoma with perineural spread to facial canal: F-18 FDG PET/CT detection. *Clin Nucl Med*. 2008;33(12):925-958. doi:10.1097/RLU.0b013e31818c4e38
14. Mlika M, Kourda N, Zidi Y, et al. Salivary duct carcinoma of the parotid gland. *J Oral Maxillofac Pathol*. 2012;16(1):134-136. doi:10.4103/0973-029X.92992
15. Jalaly JB, Sanati S, Chernock RD, Dibe DG, El-Mofty SK. Salivary duct carcinoma and invasive ductal carcinoma of the breast: a comparative immunohistochemical study. *Head Neck Pathol*. 2018;12(4):488-492. doi:10.1007/s12105-017-0882-2
16. Fan CY, Wang J, Barnes EL. Expression of androgen receptor and prostatic specific markers in salivary duct carcinoma: an immunohistochemical analysis of 13 cases and review of the literature. *Am J Surg Pathol*. 2000;24(4):579-586. doi:10.1097/00000478-200004000-00014
17. Skalova A, Stenman G, Simpson RHW, et al. The Role of molecular testing in the differential diagnosis of salivary gland carcinomas. *Am J Surg Pathol*. 2018;42(2):e11-e27. doi:10.1097/PAS.0000000000000980
18. Wenig B. *Atlas of Head and Neck Pathology*. 3rd ed. Elsevier; 2016:1003-1009.
19. D'Heygere E, Meulemans J, Vander Poorten V. Salivary duct carcinoma. *Curr Opin Otolaryngol Head Neck Surg*. 2018;26(2):142-151. doi:10.1097/moo.0000000000000436
20. Pons Y, Alves A, Clement P, Conessa C. Salivary duct carcinoma of the parotid. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2011;128(4):194-196. doi:10.1016/j.anorl.2010.12.008
21. Locati LD, Perrone F, Cortelazzi B, et al. Clinical activity of androgen deprivation therapy in patients with metastatic/relapsed androgen receptor-positive salivary gland cancers. *Head Neck*. 2016;38(5):724-731. doi:10.1002/hed.23940
22. van Boxtel W, Boon E, Weijs WLJ, van den Hoogen FJA, Flucke UE, van Herpen CML. Combination of docetaxel, trastuzumab and pertuzumab or treatment with trastuzumab-emtansine for metastatic salivary duct carcinoma. *Oral Oncol*. 2017;72:198-200. doi:10.1016/j.oraloncology.2017.06.023