1. 14 year old female with a history of atypical teratoid rhabdoid tumor now presenting with a left parotid mass.

**Diagnosis: Mammary Analogue Secretory Carcinoma**

Mammary Analogue Secretory Carcinoma (MASC) is a relatively recently described salivary gland tumor which is named for its shared morphologic and molecular characteristics with secretory carcinoma of breast. However, in salivary gland MASC actually predominates in the 5th decade with a slight male predilection. Parotid is the most common site, but other locations have been described. No predisposing risk factors are commonly noted, but this particular case represents the first MASC arising as a secondary malignancy in childhood (of note, this phenomenon has been described for mucoepidermoid carcinoma).

Histologically, these are fairly characteristic eosinophilic tumors with abundant granular to vacuolated cytoplasm often with luminal and even intracytoplasmic mucin; almost a facsimile of secretory carcinoma of breast. Growth patterns are diverse, ranging from solid, to follicular, to papillary and cystic. Lymphoid stroma is also not uncommon. Immunophenotypically, these tumors are classically strongly S100, Mammaglobin, and vimentin positive, and DOG1 weak to negative. Like secretory carcinoma of breast, MASC are defined by the t(12;15)(p13;q25) translocation that results in an *ETV6–NTRK3* fusion, which is readily testable using fluorescence in situ hybridization (FISH) or RT-PCR for the fusion transcript.

**Differential Diagnosis**

Historically MASC were identified as a unique zymogen poor subset of acinic cell carcinomas as well as adenocarcinomas and cystadenocarcinomas, not otherwise specified. With the description of this entity, the differential diagnosis is relatively limited. Acinic cell carcinoma is distinguished from MASC by the presence of true zymogen granules, weak to absent S100 and mammaglobin negativity and strong DOG1 staining. Additionally minor salivary sites are less likely for true acinic cell carcinoma. Other S100 positive ductal tumors (i.e. polymorphous low grade adenocarcinoma / cribriform adenocarcinoma of salivary gland (PLGA/CASG), canalicular adenoma) are usually readily distinguished by their morphologic features. Unlike MASC, PLGA/CASG has less abundant cytoplasm and characteristic ovoid vesicular monomorphic nuclei. Canalicular adenoma also tends to have less cytoplasm and is composed of cuboidal to columnar cells in a myxoid stroma arrayed in canalicular growth pattern. Low grade cribriform cystadenocarcinoma may mimic MASC particularly with respect to its S100 and mammaglobin expression, but is largely an ‘in-situ’ tumor with a prominent delimiting p63 positive layer of basal/myoepithelial cells. Theoretically mucoepidermoid carcinoma, particularly the oncocytic variant is in the differential diagnosis, but these are uniformly S100 and mammaglobin negative and have a more prominent p63 staining since the ‘oncocyes’ are modified intermediate and epidermoid cells.

**Behavior**
2. Core biopsy of a left parotid lesion in a 15 year old female with a ‘vascular malformation,’ ‘cellular adenomatoid nodules of thyroid,’ and a cellular neurothekeoma.

**Diagnosis: Sclerosing Polycystic Adenosis**

Sclerosing polycystic adenosis (SPAN) is a benign salivary gland lesion resembling fibrocystic change in breast. However, X-inactivation studies suggest a clonal origin. This is a tumor that predominates in the parotid, with patients usually presenting in the fifth decade, though pediatric examples exist. There is no gender predilection. To date, no syndromic association has been noted. This case demonstrates a unique constellation of tumor types, but it is not clear yet whether this patient has a heritable tumor syndrome. By report this patient was negative for germline PTEN mutations.

Morphologically SPAN is a well demarcated lesion characterized by a mixture of ductal and acinar proliferations with varying degrees of cystic change, embedded in a fibrosclerotic stroma. All ducts and acini are delimited by a basal/myoepithelial layer. SPAN shows a spectrum of morphology that is similar to that seen in fibrocystic breast lesions. In addition to sclerosing adenosis like areas, florid (occasionally atypical) ductal hyperplasia and apocrine change may be seen. Acini, when present demonstrate abnormal bright red zymogen granules. Immunostaining profiles depend on components examined. Most of the ductal elements will show S100, and SOX-10 staining in keeping with an intercalated duct phenotype, but the larger caliber apocrine foci will stain with GCDFP-15 and androgen receptor. Acini will be strongly DOG-1 positive in an apical fashion. This heterogeneous mixture of ductal and acinar elements combined with the cystic change and fibrous stroma can allow recognition, even on core biopsy.

**References**


MASC are overall indolent tumors with similar outcomes to acinic cell carcinoma, though perhaps a slightly higher rate of lymph node metastases. Only rarely do MASC undergo high grade transformation.
Differential Diagnosis

The main differential diagnostic considerations include pleomorphic adenoma, sclerosing mucoepidermoid carcinoma and salivary duct carcinoma. Unlike pleomorphic adenoma, the stroma in SPAN is not chondromyxoid and does not demonstrate a myoepithelial component. Sclerosing mucoepidermoid carcinomas do not show apocrine change or zymogen granules but instead have a prominent admixture of epidermoid, intermediate and mucous cells. As such, the p63 immunostain will actually highlight lesional cells rather than simply a delimiting layer as seen in SPAN. Salivary duct carcinoma may share phenotypic similarities with the apocrine components of SPAN, but will have more atypia and actual evidence for infiltration.

Behavior

SPAN is benign but can recur locally in about 19% of cases. Examples with salivary duct carcinoma in-situ have been reported, but only one case of progression to invasive carcinoma has been reported to date.

References


3. Incidental finding in a parotid of a 30 year old male with left parotidectomy for arteriovenous malformation.

Diagnosis: Apocrine adenosis

Isolated apocrine adenosis of salivary gland has not been reported to date to our knowledge. Unlike breast and skin adnexa, apocrine elements are not considered normal or within the spectrum physiologic change in normal salivary gland.

Apocrine change is usually seen in the context of various lesions. Aside from salivary duct carcinoma, which is defined by this phenotype, tumor types that often have apocrine differentiation include pleomorphic adenoma, SPAN, and epithelial-myoepithelial carcinoma.

Differential Diagnosis
Main differential diagnostic considerations include the aforementioned tumor types that can show apocrine change. Multiple levels should be performed to exclude an underlying tumor type to account for an apocrine proliferation. Additionally, this apocrine adenosis is distinguished from salivary duct carcinoma by the absence of uniform atypia, necrosis and infiltration. While speculative, it is reasonable to apply ‘breast like’ criteria for defining atypia or salivary duct carcinoma in-situ which usually shows cribriform growth when noted in salivary gland. Also while benign, oncocytic lesions may resemble apocrine adenosis, but do not show the decapitation secretions seen here, and these tend to have more granular cytoplasm (i.e. truly oncocytic rather than simply oncocytoid).

Behavior

Biologic behavior is unclear. While it is tempting to postulate that this could be a potential precursor lesion for salivary duct carcinoma, evidence is lacking.

References

Clonal nature of sclerosing polycystic adenosis of salivary glands demonstrated by using the polymorphism of the human androgen receptor (HUMARA) locus as a marker.

Immunohistochemical evaluation of androgen receptor, HER-2/neu, and p53 in benign pleomorphic adenomas.
DeRoche TC, Hoschar AP, Hunt JL. Arch Pathol Lab Med. 2008 Dec;132(12):1907-1

New variants of epithelial-myoepithelial carcinoma: oncocytic-sebaceous and apocrine.

4. 16 year old male with left nasal septal polyp completely excised.

**Diagnosis: Sinonasal Seromucinous Hamartoma with Early Morular Metaplasia**

Sinosal seromucinous hamartoma (SSH) is a benign glandular sinonasal lesion with a predilection for the nasal septum. This lesion occurs in all age groups and may occasionally share features with another benign sinonasal entity, respiratory epithelial adenomatoid hamartoma.

SSH are characterized by a lobular proliferation of monomorphic, mostly serous acini, with scant to moderate eosinophilic granular cytoplasm and bland nuclei. The surrounding stroma varies from myxoinflammatory, akin to that seen inflammatory sinonasal polyps to scant. Larger respiratory epithelial lined glandular spaces with hyalinized basement membrane reminiscent of respiratory epithelial adenomatoid hamartoma are seen in a subset of lesions. We have also noted a subset of SSH with squamoid or morular metaplasia as seen here. These morules are often aberrantly CDX2 positive and show accumulation of nuclear β-catenin like other morule forming lesions.
Immunophenotypically, the acinar elements are typically S100, DOG1 and SOX10 positive. Though well demarcated with rounded lobular borders, the tubules in SSH classically lack or have very few p63 positive basal/myoepithelial cells surrounding acini.

**Differential Diagnosis**

The main differential diagnostic consideration is low grade non intestinal type adenocarcinoma (non-ITAC, see also case 5). In fact some argue that low grade non-ITAC and SSH are on a continuum. It is now known that most low grade non-ITAC are indeed seromucinous and can also have morular metaplasia as well. Thus the main discriminatory features for low grade non-ITAC are larger size, true confluence of glandular elements to form solid or cribriform nests, papillary areas, and infiltrative growth, often with stromal reaction.

**Behavior**

SSH are benign and simple excision is curative. While progression from SSH to non-ITAC is plausible, it is not well documented in the literature to date.

**References**

Seromucinous hamartomas: a clinicopathological study of a sinonasal glandular lesion lacking myoepithelial cells.

A Subset of Sinonasal Non-Intestinal Type Adenocarcinomas are Truly Seromucinous Adenocarcinomas: A Morphologic and Immunophenotypic Assessment and Description of a Novel Pitfall
Purgina B, Bastaki J, Duvvuri U, Seethala RR.
Head and Neck Pathol. 2015 Feb 19. [Epub ahead of print]

5. 30 year old male with right nasal mass.

**Diagnosis: Sinonasal Non-Intestinal (Seromucinous) Type Adenocarcinoma, Low Grade with Morular Metaplasia**

Sinoonasal non-ITAC are traditionally diagnosed based on exclusionary principles, excluding intestinal type adenocarcinoma (ITAC) and named salivary type carcinomas. Synonyms for this tumor include terminal tubulus adenocarcinoma, sinonasal tubulopapillary low-grade adenocarcinoma, low grade sinonasal adenocarcinoma, and seromucinous adenocarcinoma. Non-ITAC have a wide age distribution and predominate in the fourth to fifth decades. Nasal sites predominate, but virtually all paranasal sinuses may be involved.

Low grade non-ITAC are composed of monomorphic glandular proliferations that range from a tubulolobular growth pattern seen in SSH to a more papillary arborizing architecture with psammoma bodies. Cystic change is occasionally noted as well. Nuclei are round, monomorphic
and only slightly larger than those of normal serous acini. Cells range from cuboidal to columnar in appearance. About one fourth of non-ITAC show ‘intermediate grade’ nuclei showing some size variation and occasional prominent nucleoli, but otherwise similar architecture. Non-ITAC are CK7 positive and CK20 negative. They are also usually CDX2 negative except in the rare cases in which there is morule formation. Still the CDX2 expression here is restricted to the morules and show low to moderate intensity. It has been known that most non-ITAC are S100 positive, and with the frequent co-expression of SOX10 and DOG1, these markers support a seromucinous phenotype. P63 is generally negative with the exception of squamoid morular areas.

**Differential Diagnosis**

Distinction from SSH is described above in case 4. Otherwise, the main differential diagnostic considerations include low grade papillary ITAC, nasopharyngeal papillary adenocarcinoma and named salivary tumors such as PLGA/CASG and acinic cell carcinoma. Even low grade papillary ITAC show a well-developed intestinal phenotype with resemblance to a tubulovillous adenoma of colon. These are CK20 and CDX2 positive, with variability in CK7 expression. Additionally seromucinous markers are typically negative. Nasopharyngeal papillary adenocarcinoma is a distinctive tumor with similar morphology to low grade non-ITAC. However, they show a thyroid like immunophenotype often expression TTF-1, and additionally, they are S100 negative. Recent case reports of this entity have demonstrated a spindle cell component, a finding not described in low grade non ITAC. Regarding salivary type neoplasms, PLGA/CASG are rare in the sinonasal tract and still demonstrate the distinctive ovoid vesicular nuclei seen in oral PLGA. Acinic cell carcinomas are similarly rare in the sinonasal tract and show more abundant zymogen granule laden cytoplasm. S100 tends to be weaker, and DOG1 is even more intense than seen in non-ITAC.

**Behavior**

Low grade non-ITAC behave in an indolent fashion with a 25-30% recurrence rate and only rare deaths from disease.

**References**

Sinonasal tubulopapillary low-grade adenocarcinoma. Histopathological, immunohistochemical and ultrastructural features of poorly recognised entity.

Low-grade sinonasal adenocarcinomas: the association with and distinction from respiratory epithelial adenomatoid hamartomas and other glandular lesions.

A Subset of Sinonasal Non-Intestinal Type Adenocarcinomas are Truly Seromucinous Adenocarcinomas: A Morphologic and Immunophenotypic Assessment and Description of a Novel Pitfall
Purgina B, Bastaki J, Duvvuri U, Seethala RR.
6. 78 year old female with a history of breast carcinoma with left nasal mass attached to septum.

**Diagnosis: Sinonasal Non-Intestinal (Seromucinous) Type Adenocarcinoma, High Grade**

High grade non ITAC are a more heterogeneous and less characterized group of tumors. They span a wide age range, can occur at any sinonasal subsite, and have a male predilection.

Unlike their low grade counterparts, several subtypes exist, some of which show neuroendocrine or primitive neuroectodermal features, and some of which are more ‘squamo glandular’ in appearance arising from Schneiderian papillomas. Additionally, clear cell and apocrine groups (reminiscent of salivary duct carcinoma) are also described. All high grade non-ITAC share the CK7 positive, CK20/CDX2 negative immunoprofile and show nuclear pleomorphism, necrosis, and/or high mitotic activity (5 or more per 10 high power fields). Growth patterns also vary but are most commonly solid or cribriform. Focal expression of synaptophysin or chromogranin are not uncommon. Additionally, this case demonstrates that a subset of even high grade non ITAC are indeed seromucinous and express S100, SOX10 and/or DOG1, though intensity and distribution is typically less than low grade non-ITAC.

**Differential Diagnosis**

The differential diagnosis for high grade non-ITAC is quite broad. In addition to entities discussed for case 5, the round blue cell tumor categories, pleomorphic basaloid salivary tumor types and distant metastases are all considerations. Briefly, anything other than focal neuroendocrine or heterologous (i.e. rhabdomyoblastic) elements are not acceptable in non-ITAC and may raise consideration for entities such as teratocarcinosarcoma. Solid adenoid cystic carcinoma and adenoid cystic carcinoma with high grade transformation are diagnostic considerations and will in fact often be S100 and SOX10 positive. If a myoepithelial biphasic component is retained this is useful in establishing the diagnosis of adenoid cystic carcinoma. In difficult cases assessment for MYB may be helpful. Metastases often require clinical correlation. In our case, this patient’s breast carcinoma was a small infiltrating ductal carcinoma, completely excised 13 years prior, and was ER and PR positive.

**Behavior**

High grade non-ITAC have an aggressive course even with multimodal treatment. It is not clear whether the aforementioned subgroups have any prognostic relevance.

**References**

A histologic and immunohistochemical study describing the diversity of tumors classified as sinonasal high-grade nonintestinal adenocarcinomas.
Stelow EB, Jo VY, Mills SE, Carlson DL.
A Subset of Sinonasal Non-Intestinal Type Adenocarcinomas are Truly Seromucinous Adenocarcinomas: A Morphologic and Immunophenotypic Assessment and Description of a Novel Pitfall
Purgina B, Bastaki J, Duvvuri U, Seethala RR.
Head and Neck Pathol. 2015 Feb 19. [Epub ahead of print]

7. 49 year old female with right parotid mass.

**Diagnosis: Epithelioid Hemangioendothelioma**

Epithelioid hemangioendothelioma (EHE), though rare, is well characterized. For skin/soft tissue EHE, head and neck involvement is not uncommon comprising about 15% of cases. EHE have a female predilection and occur predominantly in the 4-5th decade.

Like EHE at other sites, head and neck EHE are composed of cords and nests of monomorphic epithelioid cells embedded in a myxohyaline stroma. Tumor cells have eosinophilic cytoplasm, often eccentrically displacing nuclei. They are also often univacuolated with occasional red blood cell fragments within these vacuoles which may represent abortive lumina. Classically vasoformative channels are not well formed in EHE. EHE are positive for most vascular markers including podoplanin, but may also be positive for cytokeratin and smooth muscle actin. Several variant morphologies accompanied by translocations have now been described. For classic EHE, the t(1;3)(p36.3;q25) translocation resulting in the WWTR1-CAMTA1 fusion is characteristic. Recently YAP1-TFE3 fusions were described characterizing EHE with actual vasoformative channels and abundant granular eosinophilic cytoplasm. These tumor show immunexpression of TFE3 as expected. The pseudomyogenic variant of EHE is composed of a fasicular growth pattern, and spindled ‘rhabdomyoblast like’ cells, and tends not to have CD34 expression though CD31 and FLI-1 are retained; this is now characterized by a SERPINE1-FOSB fusion. Incidence of these variants in head and neck sites are not well characterized.

**Differential Diagnosis**

Main diagnostic considerations for EHE in the head and neck can be subdivided into carcinomas, non-vascular mesenchymal tumors, and other vascular tumors. Immunophenotype can readily resolve most of these concerns. However, in order to establish this immunophenotype, a non-epithelial tumor type must first be considered. Since a subset of EHE can express keratin and actin, and the tumor cells resemble plasmacytoid morphology in myoepithelial lesions the typical trap in head and neck sites is to accept this as sufficient for the diagnosis of myoepithelioma or myoepithelial carcinoma. However, salivary myoepithelial tumors are usually CK 5/6, S100 and p63 positive as well. Thus negativity should prompt evaluation for non-epithelial lesions. Main mesenchymal tumors in the differential diagnosis include epithelioid sarcoma and rhabdomyosarcoma, particularly for pseudomyogenic EHE. However epithelioid sarcomas are not CD31, FLI1 or ERG positive, and desmin with myogenin can help address the consideration of rhabdomyosarcoma. Regarding vascular tumors, benign lesions such as epithelioid hemangiomma (angiolymphoid hyperplasia with eosinophilia or ALHE) and epithelioid angiomatous nodule as well as epithelioid angiosarcoma on the other end of the spectrum are considerations. Epithelioid angiomatous nodule, while not uncommon in the head and neck
region, is usually small, well demarcated with an associated inflammatory component, and mainly restricted to the cutaneous region. ALHE has a predilection for head and neck sites and can present in a multinodular fashion mimicking a malignancy. However the prominent lymphoid cuff, inflammatory, eosinophil-rich milieu and the zonation from a central distorted ‘feeder’ type vessel are typical of this entity. Epithelioid angiosarcomas tend to occur in older individuals and are more pleomorphic, mitotically active and more prone to necrosis. Additionally vasoformative spaces are more complex and varied than those of EHE.

**Behavior**

EHE behaves like a borderline to low grade malignancy with a 5 year survival of over 70%. Malignant EHE is defined by mitotic activity greater than 3 per 50 high power fields and size greater than 3 cm, has a worse outcome, with a 5 year survival of ~59%. This particular case did have a prior overlying skin excision showing more mitotic activity placing this tumor in the ‘malignant’ category of EHE. Lymph node metastases may be present in about 5% of head and neck cases. This case shows extensive intraparotid nodal involvement, a finding that thus does not automatically equate to carcinoma.

**References**

Epithelioid hemangioendothelioma of the head and neck: role of podoplanin in the differential diagnosis.
Naqvi J, Ordonez NG, Luna MA, Williams MD, Weber RS, El-Naggar AK.

Pseudomyogenic hemangioendothelioma: a distinctive, often multicentric tumor with indolent behavior.
Hornick JL, Fletcher CD.

Malignant vascular tumors--an update.
Antonescu C.
Mod Pathol. 2014 Jan;27 Suppl 1:S30-8

8. 36 year old male with left deep lobe parotid mass.

**Diagnosis: Sclerosing Rhabdomyosarcoma**

Sclerosing Rhabdomyosarcoma (SRMS) is grouped with spindle cell rhabdomyosarcoma in a distinct category since both variants show morphologic and immunophenotypic overlap. This variant has a predilection for head and neck as well as extremities, but only two primary parotid cases have been described to date (including this one). Age range is broad for this variant.

SRMS demonstrates a corded infiltrative proliferation of spindled to ovoid cells with irregular nuclei and variable amounts of eosinophilic cytoplasm. Occasional strap cells may be noted. Cells often show dyshesion, clefting from the stroma, forming pseudovascular spaces. The stroma itself is characteristically acellular and densely hyalinized. These are usually negative for keratins, and will instead demonstrate strong reactivity for desmin and moderate staining for
myogenin or myoD1. Actin and CD99 are often positive as well. Unlike alveolar rhabdomyosarcoma, SRMS is not known to harbor FOXO1 translocations.

**Differential Diagnosis**

Like case 7, SRMS presenting in head and neck sites has to be distinguished from carcinomas, as well as other primary mesenchymal tumors including other variants of rhabdomyosarcoma. While there is considerable morphologic mimicry of a myoepithelial carcinoma, SRMS are typically keratin negative and invariably S100 and p63 negative. These findings should prompt consideration of non-epithelial tumors and subsequent additional work-up to include markers such as desmin and myogenin. Vascular markers can effectively exclude angiosarcoma and EHE which are also diagnostic considerations. Finally, the cored appearance and sclerosis may raise the consideration of sclerosing epithelioid fibrosarcoma. However, in addition to the aforementioned markers, MUC4 and FUS FISH can be performed if necessary to address this consideration. SRMS can be confused with alveolar rhabdomyosarcoma given the degree of cell dyshesion and clefting. However, as noted above FOXO1 FISH can help resolve this.

**Behavior**

About a fifth of patients will show distant metastases and die of disease. As the molecular pathogenesis of this variant is not well explored, rationale for distinctive therapeutic approaches in comparison to other rhabdomyosarcoma variants is not clear.

**References**

Sclerosing rhabdomyosarcoma: report of a case arising in the head and neck of an adult and review of the literature.
Robinson JC, Richardson MS, Neville BW, Day TA, Chi AC.

Sclerosing Rhabdomyosarcoma: Presentation of a Rare Sarcoma Mimicking Myoepithelial Carcinoma of the Parotid Gland and Review of the Literature.
Warner BM, Griffith CC, Taylor WD, Seethala RR.
Head Neck Pathol. 2014 Apr 8

9. 56 year old female with left parotid mass.

**Diagnosis: Adamantinoma-like Ewing Sarcoma**

Adamantinoma-like Ewing Sarcoma (AES) is an uncommon variant in the Ewing family of tumors (EFT) comprising about 5% of all EFT. AES of the head and neck region, let alone parotid are exceptionally rare.

Unlike most EFT, AES is characterized by an epithelial, specifically squamous phenotype. Growth patterns may range from nested to diffuse with variable desmoplasia. Around tumor nests, peripheral palisading and central maturation including frank keratinization may be present. Other more characteristic EFT features on the primitive neuroectodermal spectrum, namely rosettes may be focal to absent in AES. AES are typically CD99 positive, and may show some
neuroendocrine marker immunoexpression (mainly synaptophysin). However they are also positive for keratins, including high molecular weight keratins, and p63/p40. In keeping with their classification in the EFT group, these harbor EWSR1 translocations. Almost invariably, the partner in AES is FLI1.

**Differential Diagnosis**

It should be apparent by now that any sarcoma presenting in head and neck, particularly salivary sites, can easily mimic a primary or metastatic epithelial neoplasm. Additionally, for AES other round blue cell tumors enter the differential diagnosis. In salivary gland AES can mimic basal cell adenocarcinoma, and solid adenoid cystic carcinoma. However basal cell adenocarcinomas, though palisaded and positive for basal markers such as p63/p40, and CK 5/6, are biphasic tumors with a true ductal component. They also have a myoepithelial contribution. While both AES and basal cell adenocarcinoma are p63 positive, the distribution is distinctly peripheral (abluminal) in basal cell adenoma, while it ranges from random to diffuse with varying intensity in AES. Additionally most basal cell adenocarcinomas are low grade and not as infiltrative as AES. Newer markers such as LEF1 combined with nuclear β catenin are often positive in the peripheral-most layers of basal cell adenocarcinoma tumor nests. Regarding solid adenoid cystic carcinoma which can be equally infiltrative, p63 distribution is patterned in an abluminal fashion like basal cell adenocarcinoma, and the p63 positive cells co-express actin and other myoepithelial markers. Additionally the tumor cells are more angulated and hyperchromatic. Metastatic non-keratinizing squamous cell carcinoma may also resemble AES. Thus evaluation for a nodal predominant presentation along with a search for viral etiology (either EBV or HPV) may help exclude this possibility. Regarding other round blue cell tumors – neuroendocrine carcinomas of parotid and metastatic Merkel cell carcinoma can enter the differential diagnosis. However, unlike AES, these do not generally express p40, and tend to express chromogranin more frequently. Merkel cell carcinoma also has the classic ‘dot-like’ CK20 positivity, and up to 2/3 of cases harbor merkel cell polyomavirus for which immunohistochemical stains are now available. Of the other sarcomas, desmoplastic small round cell tumor (DSRCT) features as a prominent consideration given the shared desmoplasia and epithelial marker expression. However DSRCT also show desmin positivity and with the correct (C-terminus) antibody, will show WT1 reactivity as well.

**Behavior**

Collectively, non-conventional Ewing sarcomas (including large cell, spindled, AES, and pseudovascular variants) may on univariate analysis have a worse behavior than classic Ewing sarcoma. However, there is insufficient data to make this claim specifically for AES.

**References**

Morphologic and immunophenotypic diversity in Ewing family tumors: a study of 66 genetically confirmed cases.
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Histological heterogeneity of Ewing’s sarcoma/PNET: an immunohistochemical analysis of 415 genetically confirmed cases with clinical support.
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