Adenoid Cystic Carcinoma With Striking Tubular Hypereosinophilia

A Unique Pattern Associated With Nonparotid Location and Both Canonical and Novel EWSR1::MYB and FUS::MYB Fusions

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Abstract: The classification of salivary gland tumors is ever-evolving with new variants of tumors being described every year. Next-generation sequencing panels have helped to prove and disprove prior assumptions about tumors' relationships to one another, and have helped refine this classification. Adenoid cystic carcinoma (AdCC) is one of the most common salivary gland malignancies and occurs at all major and minor salivary gland and seromucous gland sites. Most AdCC are predominantly myoepithelial and basaloid with variable cribriform, tubular, and solid growth. The luminal tubular elements are often less conspicuous. AdCC has largely been characterized by canonical *MYB* fusions, with *MYB::NFIB* and rarer *MYBL1::NFIB*. Anecdotal cases of AdCC, mostly in nonmajor salivary gland sites, have been noted to have unusual patterns, including squamous differentiation and macrocystic growth. Recently, this has led to the recognition of a subtype termed "metatypical adenoid cystic carcinoma." Another unusual histology that we have seen with a wide range of architecture, is striking tubular hypereosinophilia. The hypereosinophilia and luminal cell prominence is in stark contrast to the vast majority of AdCC that are basaloid and myoepithelial predominant. A total of 16 cases with tubular hypereosinophilia were collected, forming morular, solid, micropapillary, and glomeruloid growth, and occasionally having rhabdoid or Paneth-like cells. They were subjected to molecular profiling demonstrating canonical *MYB::NFIB* (5 cases) and *MYBL1::NFIB* (2 cases), as well as noncanonical *EWSR1::MYB* (2 cases) and *FUS::MYB* (1 case). The remaining 6 cases had either no fusion (3 cases) or failed sequencing (3 cases). All cases were present in nonmajor salivary gland sites, with seromucous glands being the most common. These include sinonasal tract (7 cases), laryngotracheal (2 cases), external auditory canal (2 cases), nasopharynx (1 case), base of tongue (2 cases), palate (1 case), and floor of mouth (1 case). A tissue microarray of 102 conventional AdCC, including many in major salivary gland sites was examined for *EWSR1* and *FUS* by fluorescence in situ hybridization and showed that these novel fusions were isolated to this histology and nonmajor salivary gland location. In summary, complex and striking tubular hypereosinophilia and diverse architectures are present within the spectrum of AdCC, particularly in seromucous gland sites, and may show variant *EWSR1*/*FUS*::*MYB* fusions.

Key Words: adenoid cystic carcinoma, tubular hypereosinophilia, seromucous glands, *FUS*, *EWSR1*, *MYB*, salivary

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The classification of salivary gland tumors is ever-evolving, with new subtypes of tumors and completely novel tumors being discovered and characterized. This diagnostic expansion has largely been driven by molecular profiling and is expected to only increase as next-generation sequencing (NGS) panels grow in gene coverage and sensitivity. Among the most common salivary gland carcinomas, adenoid cystic carcinoma (AdCC) has long been seen as a fairly consistent entity, similar to

mucoepidermoid carcinoma (MEC) and acinic cell carcinoma, however, recent studies have shown numerous subtypes of MEC, including clear cell, oncocytic, sclerosing, and mucoacinar subtypes.[1–4] The latter 2 tumors have little variation in molecular signatures with MEC almost always having *CRTC1::MAML2* or, rarely, the related *CRTC3::MAML2*,[5,6] and acinic cell carcinoma almost always having *NR4A3* fusions, or rarely an *HTN3::MSANTD3* fusion.[7,8] Similarly, AdCC has largely been characterized as having *MYB* fusions, with canonical *MYB::NFIB* and *MYBL1::NFIB*.[9,10] They have not been recognized to have much variation in morphology other than solid architecture affecting grade, but not representing a defined subtype, per se.

For many years, we have anecdotally seen variations in AdCC morphology, mostly in nonmajor salivary gland sites. This has led to recognition of a novel subtype of AdCC, termed "metatypical adenoid cystic carcinoma" (M-AdCC).[11] Another unusual histology that we have encountered with a wide range of architecture, is striking tubular hypereosinophilia. Like M-AdCC cases, the main reason to highlight this is because they may not be recognized as AdCC initially. The hypereosinophilia and luminal cell prominence is in stark contrast to the vast majority of AdCC that are basaloid and myoepithelial predominant. These tumors may represent a subtype of AdCC, a completely different tumor, or a collection of unrelated and unclassifiable adenocarcinomas.

To examine this issue further, we collected cases with prominent tubular hypereosinophilia, examined their variation in morphology, and subjected them to molecular profiling and/or fluorescence in situ hybridization (FISH). We also leveraged a large tissue microarray (TMA) of 102 AdCC with typical histology and encompassing all traditional sites, specifically being well-represented for major salivary glands, to determine whether any new fusions were specific to this morphology. All cases showed striking tubular hypereosinophilia, however, there were many architectural patterns. Most cases showed canonical fusions, convincingly placing them in the AdCC spectrum; however, novel fusions were identified as well. The breadth of findings in these 16 unique cases, and the molecular profiles discovered, form the basis of this study.

MATERIALS AND METHODS

Case Selection

Based on multiple cases reviewed by and known to the authors, the pathology archives were searched for additional cases with similar tubular hypereosinophilia. A total of 16 cases with varying degrees of tubular hypereosinophilia were found with slides for review and blocks available for NGS and/or FISH. In addition, a TMA of 102 AdCC was available for *EWSR1* and *FUS* FISH testing. Of these, 5 additional cases had NGS on a whole block of tumor based on the FISH results. No other candidates with material for NGS testing were identified.

RNA Sequencing

RNA was extracted from the corresponding formalin-fixed paraffin-embedded blocks. Samples were then analyzed using the TruSight RNA Fusion Panel or SalvGlandDx, using the Illumina MiSeq system. The detailed methods are further outlined in previous publications by Freiberger et al,[8] Thompson et al,[12] and Dickson et al.[13]

FISH testing

FISH was performed in the author's labs using 2 to 4 μm thick sections incubated with dual color break-apart FISH probes (centromeric 5′-side red, telomeric 3′-side green) for *EWSR1* and *FUS* (Abbott Molecular) according to the manufacturer's protocol. This was performed on cases with fusions containing these genes identified by NGS. In addition, a TMA of 102 AdCC from numerous head and neck sites was screened for additional cases containing *EWSR1* or *FUS* break-apart signals. A total of 50 to 100 nonoverlapping nuclei were scored using a fluorescence microscope. Positive FISH was defined as at least 12% cells with break-apart and/or split signals. Positive signals, or equivocal results from the TMA with <12% break-apart signals, were then subjected to whole block NGS.

RESULTS

A total of 16 cases with striking tubular hypereosinophilia were collected for review with an age range of 33 to 89 years (average: 65.7 y). There was an equal sex distribution with 8 male and 8 female patients. The tumors sites were base of tongue (2), nasal cavity (2), maxillary sinus (2), sphenoid (1), maxilla (1), nasopharynx (1), skull base (1), external auditory canal (2), larynx (1), trachea (1), hard palate (1), and floor of mouth (1). No cases with this pattern were found in major salivary glands. The tubular hypereosinophilia ranged from large luminal pink cells, ~3 times the size of conventional luminal cells, to squamoid, rhabdoid, and even Paneth-like morphology. Some of these large luminal cells had a clear cell appearance as well. The increased size of the cells was largely due to the cytoplasm, with similar-sized nuclei to normal ductal luminal cells in conventional AdCCs. The nuclei were monomorphic, with variable open to hyperchromatic chromatin. Mitotic activity was inconspicuous and necrosis was absent. The architectures ranged from tubules to micropapillary (Fig. 1), glomeruloid (Fig. 2), luminal-cribriform, morular, and solid patterns. The morular elements had a squamoid morphology, however, there were no true squamous pearls, and no overt keratinization was identified. The morular elements were often associated with micropapillary or glomeruloid architectural patterns. There was a predominance of tubular and nonconventional morphologies in most cases (Figs. 3, 4), with typical basaloid cribriform morphology identified in some cases, but representing a minority of the tumor's volume when present (<20%). The 2 external auditory canal cases, however, were the outliers, with mostly conventional morphology and only focal tubular hypereosinophilia or Paneth-like cells (Fig. 2). The cribriform basaloid morphology was therefore ranging dramatically from minimal (<5%) to nearly 100% in the ear

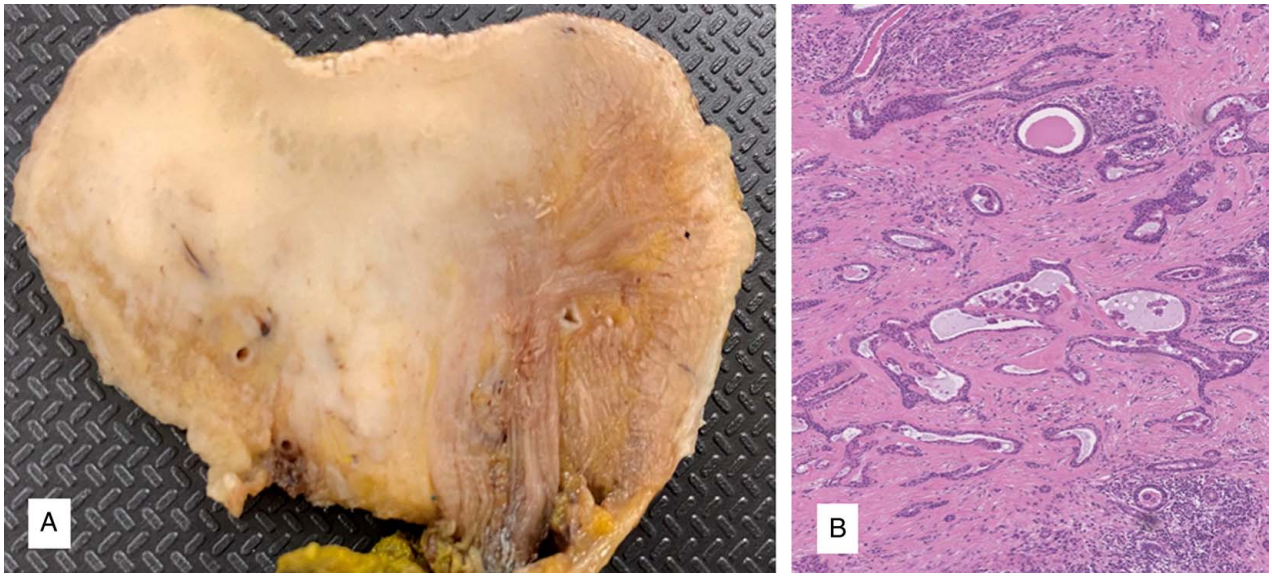

FIGURE 1. Grossly, the tumors were highly infiltrative tan-white neoplasms. This tumor in the base of tongue (case 3) can be seen to involve over half of the specimen with deep tongues penetrating the muscle (A). The tumor showed almost entirely tubular morphology with unusual micropapillary luminal architecture (B).

tumors. Most cases could still be recognized as AdCC by the overt bilayering and areas of typical tubular morphology. Perineural invasion was not common, however, when seen it had the typical appearance as is seen in conventional AdCC (Fig. 2C). The lack of perineural invasion in most cases may reflect the site or origin in unusual locations, or the small sample sizes in tumors that were sometimes only biopsied or taken in fragments. Angiolymphatic invasion was absent. NGS was successful in 13 of the cases. Of these, there were 2 *EWSR1::MYB* fusion-positive sinonasal tumors and 1 *FUS::MYB* fusion-positive base of tongue tumor. One of these cases had previous clinical evidence of FISH rearrangement of both *EWSR1* and *MYB*. The 2 *EWSR1::MYB* cases showed extensive tubular hypereosinophilia, while the *FUS::MYB* case showed among the most striking morular, micropapillary, and Paneth-like morphology (Fig. 2), and was confirmed to be *FUS* rearranged by FISH. There were 7 canonical fusions, with 5 *MYB::NFIB* and 2 *MYBL1::NFIB*

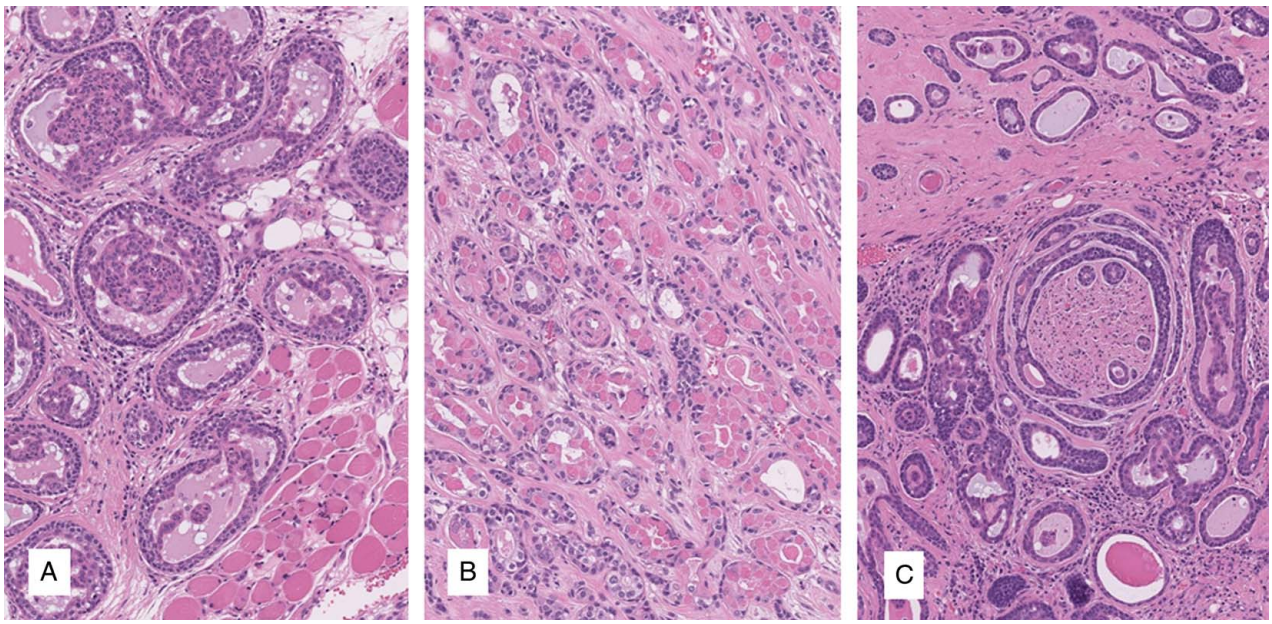

FIGURE 2. The same tumor as Figure 1 showed a novel *FUS::MYB* fusion and had a variety of unusual patterns including morular and glomeruloid luminal structures (A) and extensive luminal paneth-like cells (B). The tumor was entirely bilayered and showed a small focus of more typical AdCC tubules with perineural and intraneural invasion (C).

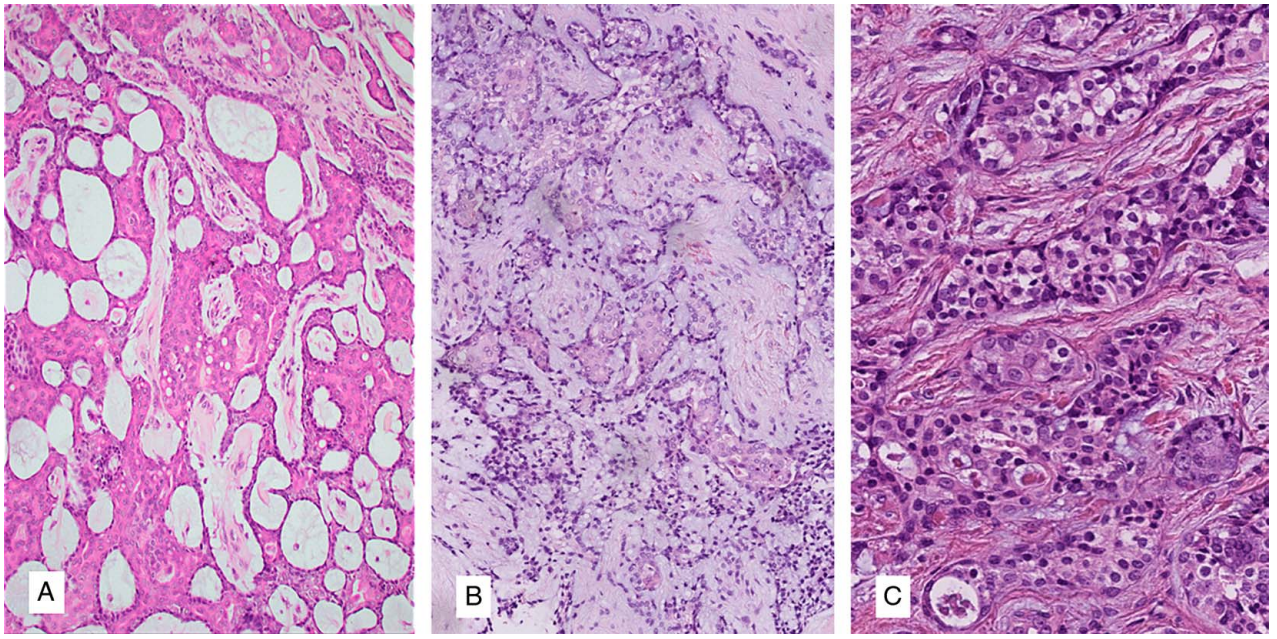

FIGURE 3. Two tumors had a related *EWSR1::MYB* fusion. Case 1 from the skull base showed tubular hypereosinophilia with small microvacuoles typical of AdCC (A). Case 2 from the sphenoid showed tubular hypereosinophilia with basaloid myoepithelial cells (B) and foci of luminal clear cells (C).

cases. There were also 3 cases with no fusions identified. A summary is provided in Table 1.

The TMA contained material from 102 AdCC with an age range of 17 to 86 years (average: 55.8 y). There were 40 males and 62 females. The tumors were located in the sinonasal tract/base of skull (n = 28), parotid gland (n = 22), oral cavity (n = 17), submandibular gland (n = 11), larynx/trachea (n = 6), orbit/lacrimal gland (n = 5), oropharynx (n = 5), sublingual gland (n = 3), external auditory canal (n = 3), lung (n = 1), and nasopharynx (n = 1). All cases were subjected to FISH for *EWSR1* and *FUS* to screen for additional cases containing the novel fusions. A total of 5 cases with equivocal FISH results (3 *FUS* and 2 *EWSR1*) were then subjected to NGS on a whole block of tumor. These 5 cases did not show any tubular hypereosinophilia on whole slides and showed no additional fusions containing *EWSR1* or *FUS*, with canonical *MYB::NFIB* (maxillary sinus) and *MYBL1::NFIB* fusions (nasal cavity), a single novel *MYB::TCEA1* fusion (parotid gland), 1 negative case (parotid gland), and 1 case failing NGS (parotid gland). There were no FISH-positive signals on the remaining TMA cases. In total, based on the number of TMA cases, and the number of conventional AdCCs in our consultation files, we believe this morphology is extremely rare and well below 1% of all AdCCs.

Immunohistochemistry was inconsistently applied to these cases across multiple labs and therefore are not described here in detail. The tumors uniformly showed bilayering with luminal and abluminal markers, such as CK7, and p63, respectively. The tubular hypereosinophilia cells were always negative for p63 even when squamoid, suggesting no true squamous morphology.

DISCUSSION

The classification of salivary gland tumors has changed significantly due to a greater understanding of the variability in morphology of these uncommon tumors established upon a backbone of reproducible molecular findings. Some of this has been achieved with painstaking case examination and nuanced description, while other findings have started with molecular discovery, and retrospective review of adenocarcinoma not otherwise specified cases or unusual cases seen in consultation. AdCC is one of the most common and deadly salivary gland cancers and has been recognized as a distinct entity for many years. The typical morphology is a basaloid cribriform predominant tumor, occasionally with bilayered tubules. Both of these morphologies represent low-grade tumors. The myoepithelial abluminal cells form the majority of the tumor and are responsible for matrix deposition that can be basement membrane-like or wispy and blue. The inner luminal cells are a minor component of the tumor and may show eosinophilic secretions. Solid areas, which may have more atypia and mitotic activity, define the higher grade tumors. Although not specifically published, there are a number of findings that have traditionally been thought to be exclusion criteria for this entity.[11] These include macrocystic growth, squamous differentiation, extensive trabecular growth, and circumscription. All of these findings, however, have recently been described in M-AdCC occurring in the sinonasal tract and skull base.[11] These were recognized as a significant pitfall with other tumors that more typically show these morphologies, and were proven with the finding of canonical *MYB::NFIB* and *MYBL1::NFIB* fusions in these cases.[11] Anecdotally, many head and neck experts have suggested that nonmajor gland sites may

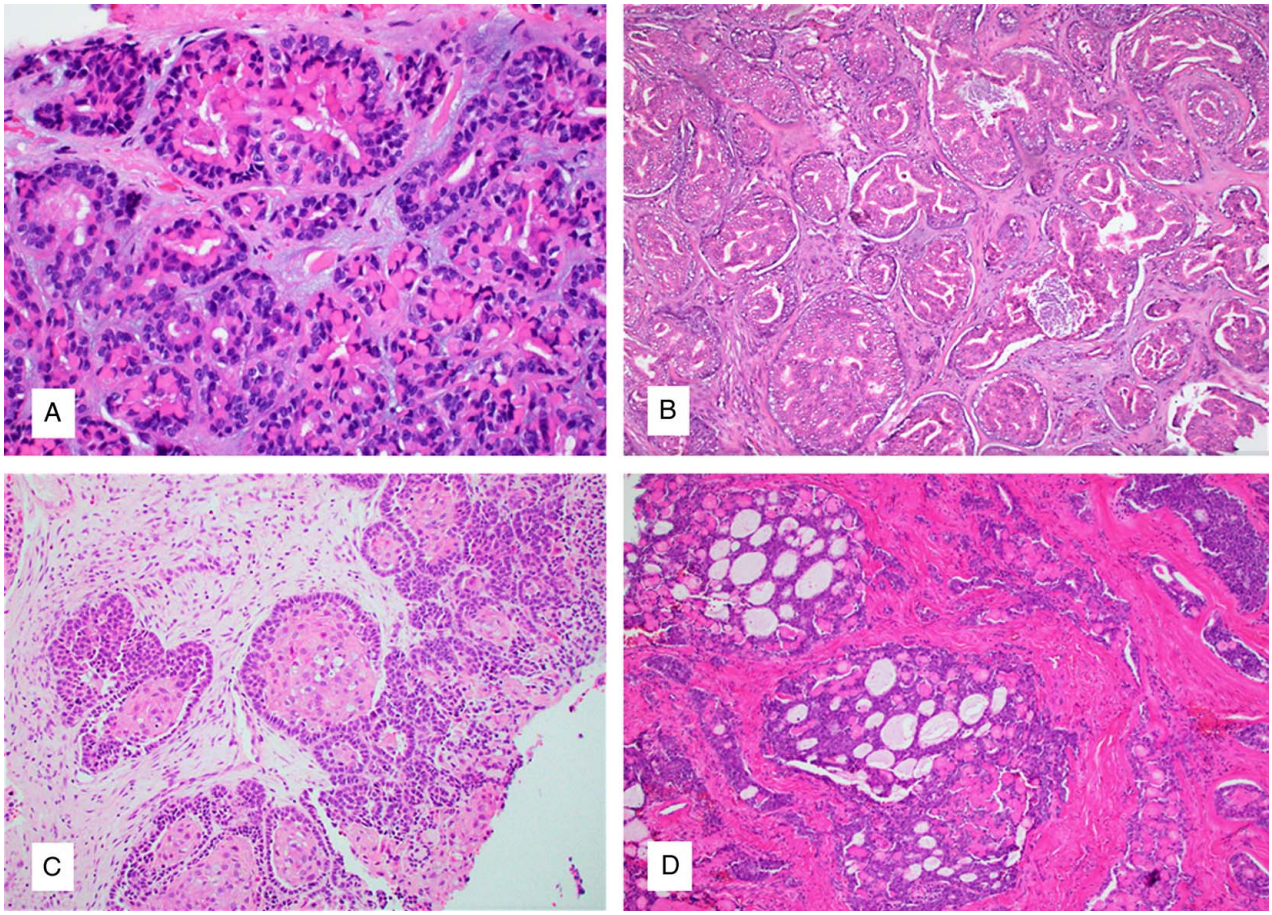

FIGURE 4. The tubular hypereosinophilia was also seen with canonical fusions and cases that were negative for fusions. A variety of morphology was seen including rhabdoid luminal cells (A) in case 15, a *MYBL1::NFIB*-positive laryngeal tumor; complex micropapillary and luminal-cribriform growth in case 13, a *MYB::NFIB*-sive maxillary tumor (B); and solid squamoid growth in case 9, a fusion negative tumor (C). This latter case had otherwise similar areas to other tumors in this cohort. Finally, a novel fusion, *MYB::TCEA1*, was seen in this conventional AdCC from the TMA with basaloid cribriform growth (D).

TABLE 1. Findings in AdCCs With Tubular Hypereosinophilia

Case no.	Age (y)	Sex	Site	Morphology	NGS and FISH results
1	70	Male	Skull base/sinonasal tract	Large tubular eosinophilic cells	*EWSR1::MYB*
2	82	Male	Sphenoid sinus	Large tubular eosinophilic and clear cells	*EWSR1::MYB* *EWSR1* FISH+ *MYB* FISH+
3	75	Female	Base of tongue	Large tubular eosinophilic cells, morules, micropapillary, and Paneth-like cells	*FUS::MYB* *FUS* FISH+
4	73	Female	Base of tongue	Large tubular eosinophilic cells	Negative
5	65	Male	Floor of mouth	Large tubular eosinophilic cells	Failed
6	75	Female	Hard palate	Large tubular eosinophilic cells	*MYBL1::NFIB*
7	71	Female	External auditory canal	Focal tubular cribriform	Failed
8	33	Female	External auditory canal	Focal Paneth-like cells	Negative
9	89	Male	Nasal cavity	Solid luminal eosinophilic nests	Negative
10	48	Female	Nasal cavity	Large tubular eosinophilic cells	*MYB::NFIB*
11	55	Male	Maxillary sinus	Large tubular eosinophilic cells	*MYB::NFIB*
12	71	Male	Maxillary sinus	Large tubular eosinophilic cells	Failed
13	58	Male	Maxilla	Micropapillary and glomeruloid	*MYB::NFIB*
14	84	Female	Nasopharynx	Large tubular eosinophilic cells	*MYB::NFIB*
15	52	Female	Larynx	Extensive luminal rhabdoid cells	*MYBL1::NFIB*
16	50	Male	Trachea	Large tubular eosinophilic cells	*MYB::NFIB*

show more variation in morphology (personal observations of the authors).

The canonical fusions have been discovered in 35% to 100% of AdCC by various authors using reverse transcriptase-polymerase chain reaction; FISH for *MYB::NFIB* and/or *MYBL1::NFIB,* or break-apart FISH for *MYB* and/or *MYBL1*; MYB RNA in situ hybridization; and NGS platforms.[9,10,14–16] Occasional classic cases are seen that are negative for these fusions using these techniques, either because of the sensitivity of these platforms for identifying the fusion, or because of alternate molecular mechanisms. These may include undiscovered fusions, rare fusions that are known but not tested for with some targeted panels, such as *NFIB::AIG1*,[15] or nonfusion events such as *NOTCH* or *TERT* mutations.[17] The fusion status is not thought to be prognostic or significantly associated with any clinicopathologic factors, however, other mutations may factor into treatment options.[17] Not uncommonly, classic cases of AdCC may lack any and all of these described molecular events.

One of the many unusual findings we have seen over the years is more significant tubular eosinophilia. This can be seen focally and be subtle or can be prominent and diffuse. The latter types we have termed "tubular hypereosinophilia." This is not to necessarily suggest a distinct new diagnostic subtype, as the morphology can vary substantially, however, we do feel that it represents a morphology that needs to be recognized as it may otherwise raise the possibility of other tumors or simply not be recognized at all on small biopsies. Anecdotally, the authors have seen this in nonparotid locations, however, the significance of this finding and whether these tumors carry the canonical AdCC fusions, had not been studied. To examine this further, we assembled 16 cases of AdCC with tubular hypereosinophilia for detailed review of morphology, and for molecular profiling. One tumor, case 2, was recognized to have an alternate *EWSR1::MYB* fusion by way of FISH rearrangement of both genes first, and the morphology was recognized retrospectively. It was subsequently sequenced to confirm the *EWSR1::MYB* fusion. Any new fusion would then be screened with FISH on a TMA of 102 conventional AdCC to search for additional cases and examine whether they are unique to this morphology. The 16 cases showed a variety of patterns of hypereosinophilia of the tubular cells. This included larger than normal cells with a size roughly 3× the size of the normal luminal cells and with greater tubular caliber. This was the most common pattern, and in general was more associated with tubular morphology, with a general lack of cribriform growth, basaloid features, or myoepithelial content (other than the abluminal cells). Most of the tumors did have some areas of typical basaloid growth, but many lacked the cribriform pattern (< 5%). None of the non–*MYB*-rearranged cases lacked cribriform growth entirely, however, as they would have been excluded due to doubt about the diagnosis. These cases could easily be confused with other tumors, as will be discussed further below. Other common patterns included solid eosinophilic areas, rhabdoid cells, Paneth-like cells, and micropapillary, glomeruloid, and squamoid morular growth. Every pattern of tubular hypereosinophilia showed an outer layer of myoepithelial cells discernible by hematoxylin and eosin alone, however, these cells were less prominent than typical AdCC.

There were 7 canonical fusions (5 *MYB::NFIB* and 2 *MYBL1::NFIB*) representing just over half of the cases (53.8%). This represents proof of principle that they are AdCC and not a distinct tumor mimic. Three cases, representing about a quarter of cases (23.1%), showed no fusion. In addition, there were 3 related noncanonical fusions, including 2 *EWSR1::MYB* and 1 *FUS::MYB* fusion. These related fusions have not been widely recognized in AdCC, however, a single reference showed the *EWSR1::MYB* fusion in a table with no additional details.[18] The *FUS::MYB* fusion is completely novel and the first description of a *FUS* gene-rearranged salivary tumor to our knowledge. This latter tumor of the base of tongue was the most morphologically divergent from typical AdCC, with complex micropapillary, glomeruloid, morular, and tubular growth, and extensive Paneth-like cells. It was confirmed with *FUS* FISH and 1 of the *EWSR1::MYB* cases was also confirmed to have both *EWSR1* and *MYB* rearrangement by separate FISH assays.

Interestingly, as noted anecdotally by the authors previously, none of the cases were seen in major salivary glands, and most were seen in seromucous glands with only occasional cases in oral cavity. The other interesting question is whether there is any significance to *MYB* being in the 5′ position in these novel fusions, instead of the more typical 3′ position of canonical fusions.[19] Since *MYB* gene overexpression is considered enough to drive adenoid cystic carcinogenesis without a novel chimeric protein,[20] it is speculated that the method of this overexpression has no material impact on the development of these cases.

No additional cases of *EWSR1* or *FUS* rearranged AdCC were found by screening the TMA of 102 AdCC, suggesting that these are indeed very rare fusions, and possibly isolated in cases with tubular hypereosinophilia. The TMA was well-represented by major salivary tumors also suggesting these fusions could be isolated to seromucous gland sites. More cases will need to be identified and screened forto determine whether these related fusions are truly limited to this alternate morphology or nonmajor salivary locations, or both. The presence of canonical fusions in more than half of the cases certainly shows this is not a direct genotype-phenotype phenomenon and these tumors belong in the AdCC category. Although the patient outcome was beyond the scope of this manuscript and not available in most cases, the tumors were highly infiltrative, and at least one metastasized to cervical lymph nodes at first presentation. At this point, it is not clear if these new fusions have any clinical importance.

The most important reason to recognize this morphology and the various patterns is the fact that these tumors may not be recognized as AdCC, particularly on small biopsies. Although they were always bilayered, it was not always obvious on hematoxylin and eosin stains. In addition, the presence of rhabdoid or Paneth-like cells,

squamoid morules, and lack of cribriform growth may suggest features seen in pleomorphic adenoma or MEC. None of the cases showed *PLAG1*, *HMGA2*, *CRTC1*, or *MAML2* alterations by molecular profiling, ruling out these diagnostic considerations, including an AdCC ex-pleomorphic adenoma as an explanation. The location outside the parotid gland also makes this unlikely, as it would be expected that the most common site for both tumors would be represented if this possibility was responsible for the unusual findings in these 16 cases.

In summary, we have described a relatively large series of AdCC with striking tubular hypereosinophilia, a predilection for nonmajor salivary gland sites, and both canonical and novel *EWSR1::MYB* and *FUS::MYB* fusions. This further expands on our anecdotal impression that AdCC does not have any true exclusion criteria, at least in seromucous glands sites. It also emphasizes how broader molecular profiling will further expand known entities in addition to identifying new ones and confirming diagnoses in typical cases.

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