Adenoid cystic carcinomas of the breast and salivary glands (or 'The strange case of Dr Jekyll and Mr Hyde' of exocrine gland carcinomas)

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ABSTRACT

Adenoid cystic carcinoma (AdCC) is a tumour with myoepithelial differentiation and characterised by the presence of a dual population of basaloid and luminal cells arranged in specific growth patterns. These tumours, regardless of the anatomical site, are characterised by expression of the proto-oncogene and therapeutic target c-KIT, and seem to harbour a specific chromosomal translocation t(6;9) leading to the fusion gene *MYB-NFIB* and overexpression of the oncogene *MYB*. However, the clinical behaviour of salivary gland and breast AdCC differs; while salivary gland lesions have a relatively high proclivity to metastasise, patients with breast AdCCs have an excellent outcome. Here the clinical, morphological and molecular features, and potential therapeutic targets of salivary gland and breast AdCCs are reviewed.

INTRODUCTION

Adenoid cystic carcinomas (AdCCs) are among the most common salivary gland malignancies but also affect other exocrine tubulo-acinar glands[1-7] such as the breast.[8] Despite the long recognised morphological similarities of tumours arising in these two glandular structures and the fact that these tumours harbour a recurrent chromosomal translocation,[9] AdCCs of the salivary glands and the breast differ in incidence and clinical behaviour. Here, we review the clinical, morphological and molecular features, and potential therapeutic targets of salivary gland and breast AdCCs.

DEFINITION, CLASSIFICATION AND OVERVIEW OF ADENOID CYSTIC CARCINOMAS

The term cylindroma, the pathological entity later called 'adenoid cystic carcinoma', was coined by Billroth[10] to describe a salivary gland tumour composed of entwined cylinders of hyaline stroma and epithelial cells (indeed the illustrations from Billroth's study[10] depict the typical architectural pattern of cylindromas/AdCCs, and the cribriform structures with pseudoglands found in AdCCs. The term adenoid cystic carcinoma (carcinoma adenoides cysticum) of the salivary glands was first used by Ewing (1919)[11] and applied by Geschickter in 1945 to tumours of the breast.[12] Since then, AdCCs have also been described in several other organs such as lacrimal glands, auditory canal, upper respiratory tract and lung, digestive tract, skin, prostate and lower female genital tract.[1-7]

AdCC belongs to the subgroup of tumours of the myoepithelial lineage and is defined as a tumour where both epithelial (luminal) and myoepithelial (basaloid) cells are neoplastic (figure 1). Multiple architectural patterns have been reported (eg, cribriform, tubular, trabecular and solid) in both mammary and salivary glands, and generally a mixture of different growth patterns are found in AdCCs.[1 14] The cribriform growth pattern is the most characteristic and features variably sized and usually smoothly contoured islands of neoplastic cells arranged to compose pseudolumens (which are not true glandular lumens but represent stromal invaginations) and true glandular spaces (formed by the epithelial cells) giving rise to a 'sieve-like' appearance (figure 1).[1 14] These spaces are filled with eosinophilic hyaline material (Periodic acid-Schiff (PAS) positive, diastase resistant), and/or lightly basophilic myxoid substance (Alcian blue positive): these materials have been demonstrated to represent duplicated basal lamina and glycosaminoglycans by ultrastructural studies (see Cheuk and Chan[1] and Bennett et al[15] and references therein). Within the cribriform islands, there are occasional true narrow glands lined by cuboidal cells with eosinophilic cystoplasm[1] (see figure 1). Histological variants are the glandular (or tubular), reticular (or trabecular) and solid growth patterns (figure 1). The tubular variant is characterised by glandular spaces of elongated tubules lined by epithelial cells and surrounded by single or multiple layers of basaloid cells; the glandular lumens are either empty or contain secretion. In the trabecular variant cells are arranged to form small nests,[14] whereas the solid variant is composed of island and sheets of closely packed basaloid cells, with very few or even no pseudocystic spaces; few true glandular spaces can be found.[1]

The two distinct cells types of AdCCs, basaloid and luminal, are best appreciated by immunohistochemical staining (table 1). The basaloid cells express basal cytokeratins (Cks) such as Ck14 and Ck17, vimentin, S-100 protein, actin, calponin and p63. In addition, strong nuclear and cytoplasmic immunoreactivity of maspin, a mammary inhibitory serine protease, has been described in the myoepithelial component of a series of AdCCs of the breast.[16] The epithelial cells show strong positivity for luminal cytokeratins such as Ck7, for CEA, EMA and CD117 (c-KIT).[1 8 17]

The stromal hyaline material is best highlighted by staining for collagen IV and laminin. In addition, PAS and Alcian blue staining may help differentiate the material present in true glandular lumens and pseudolumen, respectively (see above).[1 8]

Figure 1 Representative micrographs of the different variants of adenoid cystic carcinoma (AdCC). Breast AdCC showing a mixture of cribriform (A), tubular (B), trabecular (C) and solid (D) growth patterns. Examples of grade 1 (I), grade 2 (II) and grade 3 (III) AdCCs, according to the grading system proposed by Ro et al.[13]

HISTOLOGICAL SUBTYPES

HISTOLOGICAL GRADE
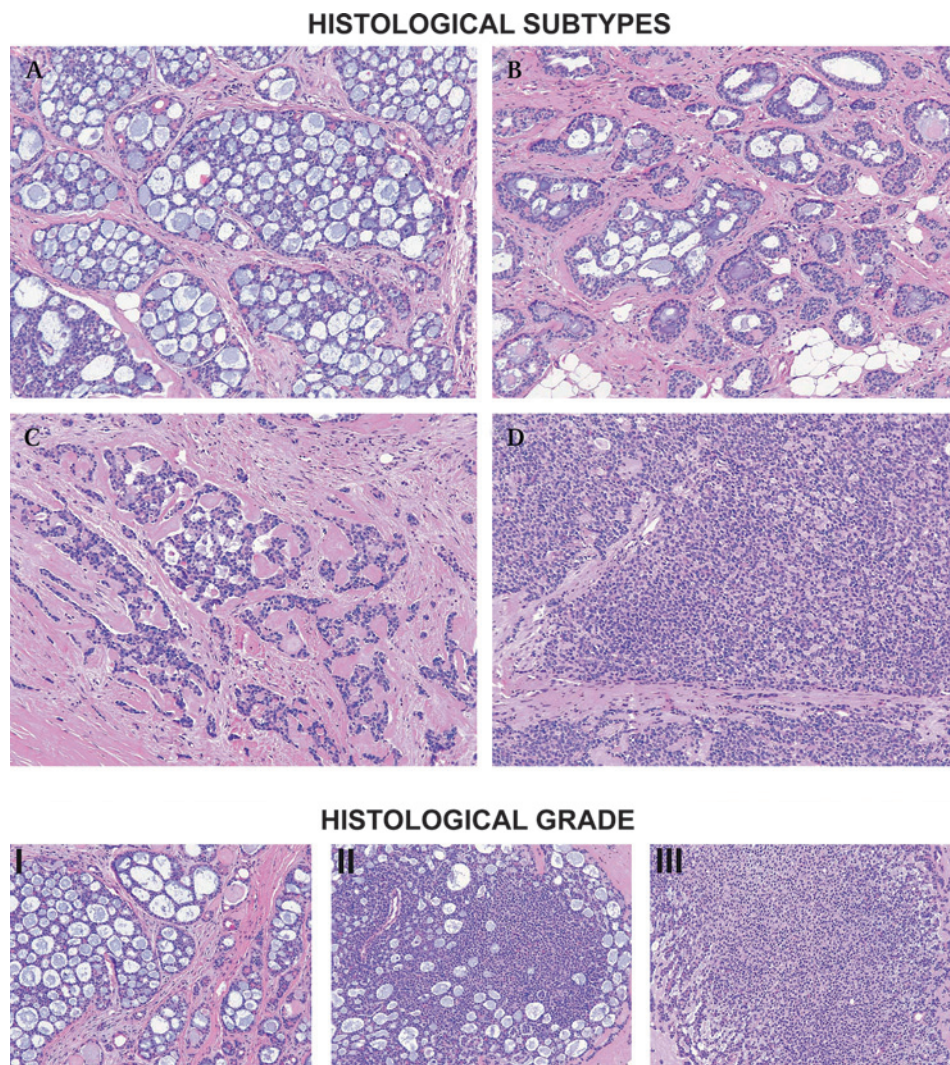
ADENOID CYSTIC CARCINOMAS OF THE SALIVARY GLANDS
Clinical and morphological features

AdCCs are part of the malignant epithelial tumours of the salivary glands and have been recognised as a specific variant of adenocarcinoma of the salivary and mucous glands since 1853.[18 19] AdCC affects patients preferentially in the fourth to sixth decade of life, with a slight female predominance (about 3:2).[1 17] The parotid gland, submandibular gland and the palate are most commonly involved,[1 17] however minor salivary glands in the oesophagus can also be affected.[20]

Table 1 Detailed immunophenotypical characterisation of the two distinct cell types of adenoid cystic carcinoma

Marker	Luminal/ epithelial	Basal/ myoepithelial
Cytokeratin 7	+++	−
Cytokeratin 14	−	+++
Cytokeratin 17	−	+++
Vimentin	−	+++
p63	−	+++
Maspin	−	++
Laminin	−	++
Fibronectin	−	++
c-KIT(CD117)	+/+++	−
CyclinD1	+/+++	−
β-Catenin nuclear	<5%	<5%

AdCCs account for about 10−15% of all parotid malignancies,[21] usually present as a slow-growing swelling, and, because of the propensity for perineural invasion, pain may be present (table 2).[1 24] In advanced cases, fixation to skin or deeper tissues can occur.[1] Owing to its growth pattern, it should be also noted that at time of presentation these tumours have often invaded beyond the clinically apparent borders.[25−33] AdCC of the salivary gland is a slow-growing but aggressive cancer which is reflected by the good short-term but very poor long-term outcome of patients with this disease.[1 34] The 5-year survival is about 60−75%, while the 10-year survival drops to 30−54%; most patients eventually die of disease after multiple local recurrences and development of distant metastases (distant metastases are more common than regional lymph-node involvement).[32 35 36]

Histologically, AdCC of the salivary glands presents variable combinations of the three main growth patterns (ie, cribriform, tubular and solid) in each individual case. The cribriform is the most characteristic and is almost invariably found, at least focally.[1] Cytologically, the basaloid cells constitute the major cell population, showing mild nuclear pleomorphism and few or no mitoses; in the solid variants these cells usually show a more pleomorphic appearance and mitoses are more commonly found.[1]

Salivary gland AdCCs are graded using a specific three-tier grading system, originally proposed by Szanto et al[18] in 1984, which is solely based on the main type of growth pattern present

Table 2 Salivary gland and breast adenoid cystic carcinomas face to face (based on various references[1 8 14 15 17 22 23])

	AdCC salivary glands	AdCC breast
Prevalence	10—15% of parotid carcinomas	0.1—1% of all breast cancers
Clinical presentation	Slow-growing swelling	Mass lesion, occasionally painful
Gross findings	Apparently well defined lesion, however often invading beyond clinically apparent borders	Well defined lesion, with rounded borders (although microscopically evident invasion of peri-tumoural tissues is often found)
Histological growth pattern		Cribriform (classic variant) Glandular (=tubular) Trabecular (=reticular) Solid
Perineural invasion	Very common	Rarely found
Lymph node metastasis	Common	Rare
Distant metastases	Common (up to 50% of the patients)	Rare, mainly visceral organs involved
Pre-invasive and associated lesions	NA	MGA, 'atypical' MGA
Associated lesions	NA	In situ and invasive carcinomas, tubular adenosis, microglandular adenosis
Survival at 10 years	30—54%	>90%
Therapeutic approach	Radical surgery for local disease Cisplatin usually employed with response rates of ~30%	Surgical excision

AdCC, adenoid cystic carcinoma; MGA, microglandular adenosis; NA, not applicable.

in the tumour. Grade 1 AdCCs are well differentiated and composed of tubular and cribriform patterns without solid components; grade 2 AdCCs are characterised by a pure cribriform pattern or mixed with less than 30% of solid areas; and grade 3 AdCCs are tumours with marked predominance of the solid pattern.[18] This histological grading system has been shown to be associated with prognosis in retrospective studies.[1 18 37 38]

Recent studies have reported that some low-grade salivary gland carcinomas, including AdCC, can undergo 'dedifferentiation'.[39–41] This histological variant would show two components, a conventional low-grade AdCC and a high-grade 'dedifferentiated' carcinoma, which can be either undifferentiated carcinoma or poorly differentiated adenocarcinoma. Dedifferentiation is a well recognised phenomenon in bone and soft tissue tumour pathology[42] and is generally associated with a poor prognosis. In AdCCs it is an extremely rare event (11 cases reported to date), whose clinical behaviour and molecular characteristics are still not entirely understood,[43] even though recent data seem to support a more aggressive clinical behaviour of dedifferentiated AdCCs.[43]

Molecular features

The defining molecular feature of AdCCs of the salivary glands and breast appears to be the presence of a recurrent chromosomal translocation t(6;9)(q22–23;p23–24), which generates a fusion transcript involving the genes MYB and NFIB.[9] This translocation is described in detail below.

AdCCs of the salivary glands have a stable genome.[44] TP53 mutations[45] or p53 nuclear expression have been reported,[46–48] but in small studies and with discrepant results (see table 3).[45 46] The presence of aneuploidy appears to be less common in the cribriform variant (16%) than in the solid lesions (67%, table 3).[53] Interestingly, a TP53 point mutation and p53 expression have been demonstrated in the dedifferentiated component of two dedifferentiated AdCCs, together with HER2 overexpression and a high proliferation index.[43]

Loss of heterozygosis (LOH), comparative genomic hybridisation (CGH) and microarray-based CGH studies show conflicting results. Cytogenetic analysis of AdCCs of salivary glands showed deletions of 6q and 12q as well as rearrangements involving chromosomes 6q and 9p.[65] Recently, high-resolution CGH analysis showed that bronchial and salivary AdCCs harbour low levels of genetic instability with few copy number alterations or high-level amplifications. Recurrent gains included 7p15.2, 17q21–25 and 22q11–13, and recurrent losses included 1p35, 6q22–25, 8q12–13, 9p21, 12q12–13 and 17p11–13.[61] In addition, Rao et al have recently shown that deletion of 1p32–p36 holds prognostic significance in these lesions.[64] Given the rather pervasive presence of recurrent regions of deletions, some have studied the possible involvement of tumour suppressor genes: the minimal region of deletions on chromosome 9p contains CDKN2A and CDKN2B; other possible candidate tumour suppressor genes map to 6q[75] and 12q.[76]

Gene amplifications have been investigated, however studies have yielded conflicting results. The majority of studies where gene amplifications were investigated using fluorescence in situ hybridisation (FISH) or CGH have reported a low prevalence of gene amplifications. The only report that identified frequent amplification of ERBB1, CCND1 and PIK3CA (67%, 46% and 38%, respectively) in AdCCs relied on a PCR-based method,[62] which is known to be prone to artefacts when formalin fixed paraffin embedded (FFPE) samples are analysed. Bernheim et al[61] and Greer et al[63] have recently identified amplifications of MDM2 (12q15), CCND1 (11q13.3) and CTTN (11q13.3) using FISH (table 3); it should be noted, however, that these amplifications affected less than 5% of cases. On the other hand, CCND1 overexpression seems to be more pervasive than CCND1 amplification, as it is found in up to 90% of cases.[63]

Apart from the recurrent chromosomal translocation described above, additional translocations have been found in single cases of AdCCs (see table 3)[55 57 59]; however neither the genes involved in these translocations nor their recurrence frequency have been determined.

Two studies have analysed the gene expression profiles of AdCC in salivary glands as compared to normal salivary gland tissues and an AdCC cell line (ACC3): unsupervised hierarchical cluster analysis showed AdCCs separated in three different groups, and interestingly, these groups were not correlated with histological grade.[67] Overexpression of several genes encoding transcription factors was demonstrated,[67] and among them, SOX4 was found to be up-regulated in both studies.[66 67] Patel et al showed that genes associated with morphogenesis, neurogenesis, proliferation, apoptosis, a group of genes encoding extracellular matrix proteins and basement membrane components seem to characterise AdCCs. In addition, Frierson et al[67] found epsilon and frizzled-7, both members of the Wnt/β-catenin signalling

Table 3 Summary of genomic features reported in adenoid cystic carcinomas of breast and salivary glands

	AdCC salivary gland	AdCC breast
TP53 mutation	40—100% (higher prevalence in solid variants)[45] *	NA
p53 nuclear expression	Reported between 17%[46—48] and 87%[48]	50% (0[49]—100%[50] †)
Other mutations	Contradictory information about *KIT* mutations. Most studies failed to identify mutations, while one study using FFPE tissues reported multiple mutations[51]	*PTEN* and *PIK3CA* (case report)[52]
Aneuploidy	16% (cribriform variant) to 67% (solid variant)[53]	<10%[54]
Recurrent translocation and cloned fusion transcript	t(6;9)(q22—23;p23—24)[9 55 56] *MYB-NFIB*[9]	t(6;9)(q22—23;p23—24) *MYB-NFIB*[9]
Translocations in single cases	t(6;12)(p21;q13)‡ [57] t(6;14)(q22;q11)[58] t(6;9)(q23—q25;p22—p24)[55 59] t(6;15)(q25;q15)[60] t(1;9)(q21;p21—22)[55] der(9)i(9)(q10)inv(9)(q12q13)[55] der(X)t(X;9)(p21;p22—23)[55]	NA
Gains	7p15.2, 17q21—25[61]; 8p, 9q, 14q, 15q, 16q, 20p, 20q§	6p, 8q, 14q, 16q, 20p, 20q§
Amplifications	*ERBB1*, *CCND1* and *PIK3CA* and their co-amplification (by PCR method)[62]; *CCND1*, *MDM2*, *CTTN* (by FISH)[61 63]	Not reported
Losses/deletions	1p32—p36[64]; 6q, 9p, 12q[65]; 1p35, 6q22—25, 8q12—13, 9p21, 12q12—13 and 17p11—13[61]	2q, 6q, 15p, 16q, 19q**
Transcriptome	Up-regulation of genes related to morphogenesis, neurogenesis, proliferation, apoptosis, extracellular matrix proteins and basement membrane,[66] transcription factors (SOX-4)[66 67]	Basal-like subtype[49]
Oncogenes overexpressed¶	c-KIT (CD117),[68—70] CCND1, Cortactin,[63] MDM2[61] and pAKT[61 71]	c-KIT (CD117)[49 51 72—74]

*Performed with nucleic acids extracted from FFPE tissues.
†p53 immunohistochemical analysis using pressure cooking antigen retrieval.
‡Translocation described in one case of AdCC and one case of polymorphous low-grade adenocarcinomas.
§Fulford, Reis-Filho and Lakhani (unpublished observations).
¶As defined by immunohistochemistry.
AdCC, adenoid cystic carcinoma; IHC, immunohistochemistry; NA, not applicable.

pathway, to be up-regulated in AdCCs compared to 175 other carcinomas from 10 anatomical sites.

ADENOID CYSTIC CARCINOMAS OF THE BREAST
Clinical, morphological and immunohistochemical features
After Geschickter's description of 'adenocystic basal cell carcinoma' of the breast,[8] three adenocystic basal cell carcinomas were reported by Foote and Stewart in 1946,[3] but it was only two decades afterwards that Galloway[77] at the Mayo clinic described the first series of mammary adenoid cystic carcinomas.[8] Since then several groups have described AdCCs of the breast; however due to the relative rarity of this tumour type, most studies are in the form of case reports or small cohorts.

The existence of AdCC in the breast has been questioned, given its morphological similarity with cribriform carcinoma[22 78]; however, immunohistochemical and ultrastructural studies have eventually proven the existence of true AdCC in the breast (see below), which is now recognised as one of 17 histological special types of breast cancer by the World Health Organization.[15 21—23 79]

AdCCs account for 0.1—1% of all breast cancers[8 15 23]; they are usually diagnosed in adult female patients as unilateral painful masses.[8 15 23] This associated pain has been suggested to be due to the contractile myoepithelial component of these tumours, as perineural invasion is not commonly seen in these lesions (table 2).[8 15] All quadrants seem to be affected, with a particular trend for the peri-areolar region.[8] The most striking feature of AdCCs of the breast, which is in stark contrast with AdCCs of salivary glands, is the excellent long-term prognosis (table 2): a 90—100% 10-year survival rate is reported, and lymph-node metastases are rare, as well as distant metastases, which affect mainly visceral organs.[15 54]

AdCC can be found in conjunction with other breast lesions, including ipsilateral and controlateral in situ and invasive carcinomas.[15] In addition, recent studies have noted an association between AdCC and microglandular adenosis (MGA),[80—83] and some authors have suggested that AdCC may develop in a background of and in continuity with MGA. Following this hypothesis there would be a spectrum of lesions with a trend of progression, encompassing MGA, 'atypical' MGA (also known as 'in situ AdCC') and invasive AdCC.[80] An association between AdCC and tubular adenosis (TA) has also been reported in one study, but the molecular analysis performed on these two lesions failed to provide evidence of molecular evolution from TA to AdCC.[14]

The variety of growth patterns described for AdCCs of the salivary glands is also found when this tumour arises in the breast: the classic cribriform pattern, as well as the glandular, trabecular and solid variants.[8] A sebaceous differentiation is found in up to 14% of cases, and foci of adenosquamous differentiation may also be encountered.[8 84]

In a way akin to salivary gland AdCC, breast AdCCs are graded according to the proportion of solid growth: cases with either cribriform or glandular pattern are considered low grade/G1 tumours, cases with <30% of solid elements are labelled as G2, whereas cases showing >30% of solid growth are classified as high grade/G3 tumours (figure 1).[8 13] Ro et al[13] reported this grading system to be clinically meaningful, as in their series, tumours with solid components (G2 and G3 cases) were more likely to develop recurrences; in addition, in the same cohort, the only patient who experienced metastases was affected by a high-grade tumour. It should be noted however that histological grade defined by this system was not associated with outcome in two other studies.[85 86]

Other authors[72] have suggested the proliferative indices to be of some relevance as they showed greater values in high-grade when compared with low-grade lesions; however proliferative activity was not found to be significantly related to prognosis.[85]

Phenotypically, AdCCs are described as hormone receptor negative carcinomas (table 4). In the series of 18 cases analysed by Azoulay et al,[73] neither oestrogen receptor (ER) nor progesterone receptor (PR) expression was identified. Similar findings have been reported in other independent series (table 4).[49 50 74]

One study[72] reported that 15% and 10% of cases were positive for ER and PR, respectively (table 4). In contrast, Arpino et al[54] demonstrated the presence of ER and PR expression in up to 46% (13/28) and 36% (10/28) of cases, respectively (table 4). Although this cohort represents one of the largest series of AdCCs reported to date (n=28), it should be noted that the cases were collected from different institutions and did not undergo a central review; hence, it cannot be formally ruled out that a substantial number of cases included in that study were cribriform carcinomas, which are usually ER and PR positive. In addition, it should be noted that dextran-coated charcoal assay,[87] instead of immunohistochemistry, was used to assess positivity for ER and PR and only 85% agreement between the two techniques is reported.[88] The use of the dextran-coated charcoal assay for ER and PR assessment of AdCCs is particularly problematic, given that normal breast lobules and ducts are often entrapped within the bulk of AdCCs, which may lead to false positive results.

Molecular features

In a way akin to salivary gland AdCCs, breast AdCCs consistently display the recurrent chromosomal translocation t(6;9)(q22−23;p23−24), which generates fusion transcripts involving the genes MYB and NFIB.[9] This translocation is described in detail below.

Although microarray-based gene expression profiling has been extensively applied to the study of breast cancer, most of these analyses ignored the histological special types of breast cancer (reviewed in Weigelt et al[89] and Weigelt and Reis-Filho[90]), and there is paucity on the transcriptomic features of AdCCs. The molecular subtypes of breast cancer (ie, basal-like, HER2, luminal A, luminal B and normal breast-like), which provide a widely used working model for a breast cancer molecular taxonomy, have been identified by microarray analysis of only the most common types, invasive ductal and invasive lobular carcinomas.[91−93] This molecular classification was shown to be of prognostic significance, with tumours of luminal A subtype being associated with the best outcome, and tumours of basal-like or HER2 subtype with the worst outcome.[91 94]

To date, only one study has formally investigated the transcriptome of breast AdCCs. Using microarray-based gene expression profiling, Weigelt et al[49] analysed a series of 113 tumours from 11 special histological types of breast cancer, including four AdCCs. Unsupervised hierarchical cluster analysis showed that AdCCs clustered together with metaplastic and medullary carcinomas, whose similar gene expression patterns were also reflected at the immunohistochemical level (triple negative phenotype; ie, lack of ER, PR and HER2; low levels of Ck19, AR and Ck8/18; high levels of CD117, vimentin, S100, Ck14 and Ck5/6 expression). In addition, molecular subtype analysis using a single sample predictor (ie, centroids)

showed that two AdCCs were of basal-like and two AdCCs of normal breast-like phenotype, a molecular subtype which is currently considered to be an artefact of sample representation (ie, high content of normal tissue contamination).[95] Indeed, molecular subtype assignment by hierarchical clustering showed that AdCCs consistently displayed a basal-like phenotype, as did medullary and metaplastic carcinomas. These results support earlier immunohistochemical observations by Azoulay et al,[73] that breast AdCCs lack expression of ER, PR and HER2 (ie, triple negative phenotype) and express basal cytokeratins (Ck5/6). These observations illustrate the heterogeneity of basal-like breast cancers and emphasise that triple negative and basal-like breast cancer is not a single entity, but rather a spectrum of lesions. Although the majority of triple negative and basal-like breast cancers are high grade cancers (ie, medullary carcinomas, grade 3 invasive ductal carcinomas of no special type (IDC-NSTs), metaplastic carcinomas and apocrine carcinomas[49 73 96−99]), there is a subgroup of low grade tumours with indolent clinical behaviour that also display a triple negative and basal-like phenotype (ie, AdCCs and secretory carcinomas). Contrary to high grade triple negative and basal-like breast cancers,[100] which have been shown to harbour TP53 mutations in >80% of cases,[101] two studies have reported that p53 nuclear expression is either absent[49] or seen in 25% of AdCCs[102]; on the other hand, one study reported p53 expression in 6/6 AdCCs analysed.[50] Furthermore, AdCCs do not appear to be more prevalent in BRCA1 germ-line mutation carriers.

There is not only a paucity of data on transcriptomic but also on the genomic features of AdCC of the breast. Cytogenetic analyses of a few cases showed 46,XX,t(4;4)(q21;q35),t(5;11)(q13;q21), 46,XX,+1,der(1;16)(q10;p10)[103] and 46,XX,inv(9).[65] Aneuploidy is reported in less than 10% of cases.[54]

In a recent case report of a 76-year-old woman affected by a breast AdCC with a kidney metastasis, molecular genetic analysis of the primary and metastatic tumour revealed both a PTEN and a PIK3CA mutation.[52] These findings led the authors to speculate that PTEN and PIK3CA mutations may be responsible for the unusually aggressive course of this particular AdCC and suggested identified novel molecular targets for therapeutic intervention. Further studies on larger cohorts are needed to confirm the prevalence of these mutations and their biological role in AdCC.

The limited molecular features of breast AdCC available suggest that these tumours have a relatively stable genome and are characterised by a recurrent chromosomal translocation involving MYB and NFIB. Although AdCCs are of triple negative and basal-like phenotype, a diagnosis of breast AdCC should not necessarily prompt the use of systemic chemotherapy, given the excellent prognosis of patients with this tumour type.

Table 4 Overview of data reported on the expression of prognostic and predictive factors, p63, basal cytokeratins and c-KIT in adenoid cystic carcinoma of the breast

	Trendell-Smith et al, 1999[50] (N = 6)	Arpino et al, 2002[54] (N = 28)	Mastropasqua et al, 2005[72] (N = 20)	Crisi et al, 2005[74] (N = 6)	Azoulay et al, 2005[73] (N = 18)	Weigelt et al, 2008[49] (N = 4)
ER	0%	46%	15%	0%	0%	0%
PR	0%	36%	10%	0%	0%	0%
HER2	0%	NA	0%	0%	0%	0%
p63	NA	NA	85%	NA	100%	50%
Cytokeratin 5/6	NA	NA	NA	NA	100%	75%
c-KIT (CD117)	NA	NA	95%	100%	100%	100%

ER, oestrogen receptor; NA, not available; PR, progesterone receptor.

MOLECULAR COMPARATIVE PATHOLOGY AND THERAPEUTIC INSIGHTS FOR ADCC: FACTS AND ARTEFACTS
c-KIT: therapeutic target or unjustified hope?

The gene *KIT* maps to 4q11–q12 and encodes c-KIT (CD117), a type III transmembrane tyrosine kinase receptor, which is activated by mutations in gastrointestinal stromal tumours and melanomas. Tumours harbouring *KIT* mutation but not over-expression of wild-type c-KIT can be targeted by the small molecule inhibitor imatinib mesylate (Gleevec, Novartis) and sorafenib (Nexavar, Bayer).

c-KIT has been shown to be expressed in up to 100% of AdCCs of the breast[49 51 72–74] and in 80–100% of AdCCs of the salivary glands arising from the head and neck.[68–70] These observations have prompted several groups to investigate whether imatinib would be a valid therapeutic option for those lesions arising in salivary glands. Bold claims were made in 2005 in a study by Faivre et al,[104] showing a remarkable response to imatinib treatment in a patient affected by AdCC of salivary glands. These data could, however, never be confirmed by subsequent clinical studies which failed to identify objective clinical responses in patients with AdCC treated with imatinib.[69 105 106] In contrast with Faivre et al,[104] there are descriptions of progression of metastatic AdCC under treatment with imatinib (table 5).[105] These disappointing results should not come as a surprise, given that activating *KIT* mutations, the determinant for response to imatinib treatment,[109] have been repeatedly reported to be vanishingly rare in these cancers.[69 70 104 105] Last year, however, Vila et al[51] demonstrated the presence of multiple *KIT* mutations in AdCCs and even multiple mutations in single cases. Owing to the small number of tumours analysed (extraction of DNA was successful in only 8/14 cases) and, most importantly, to the type of sample subjected to mutation analysis (ie, FFPE samples), these findings needs to be confirmed in larger cohorts using optimally processed samples (ie, fresh/frozen samples).

Taken together, the balance of evidence available to date suggest that c-KIT may not constitute a potential novel therapeutic target for AdCC.

A translocation in common

Persson et al[9] have recently shown that breast, salivary, lachrymal and ceruminal gland AdCCs harbour a recurrent specific translocation t(6;9)(q22–23;p23–24). This genetic alteration had already been described more than 10 years ago, by the same group, as characteristic of salivary glands. However, the fusion gene partners in this translocation have only now been identified: the oncogene *MYB* on chromosome 6q22–q23 and the transcription factor *NFIB* on chromosome 9p23–p24.[9] *MYB* maps to chromosome 6q22–q23 and encodes a transcription factor with an N-terminal DNA binding domain, a centrally located transcription activation domain, and a C-terminal negative regulatory domain, which plays a pivotal role in the control of cell proliferation, apoptosis and differentiation. It is highly expressed in immature, proliferating cells, fetal salivary gland; however it is down-regulated as cells become more differentiated.[9] In the t(6;9)(q22–q23;p23–p24), the exon 14 of *MYB* is fused to the last coding exons of *NFIB*, most often due to breakpoints in *MYB* intron 14 and in *NFIB* intron 8. This translocation was shown to produce distinct types of fusion transcripts due to splice variations of the *MYB* gene. The common denominator of these genetic aberrations, however, was a deletion of exon 15 of *MYB* and its 3′-UTR, which contains several highly conserved target sites for miR-15a/16 and miR-150 microRNAs. In normal and cancer cells, these miRNAs have been shown to down-regulate the expression of MYB. Consistent with this hypothesis, transfection of leukaemic cells with premiR-15a/16 and premiR-150 resulted in a significant down-regulation of MYB mRNA expression, whereas transfection of ACC cells did not alter the expression levels of MYB significantly.[9]

Despite the limited number of samples analysed so far,[9] this is the first fusion transcript identified in AdCCs. Although the use of split apart probes for the identification of this translocation are unlikely to be used in diagnostic practice, due to the characteristic histological features of AdCC, one can envisage that these probes may help reclassify some tumours with features overlapping with those of AdCC or mixed salivary gland tumours.

Table 5 Summary of clinical trials where imatinib mesylate (Gleevec, Novartis) was tested in patients with adenoid cystic carcinoma of salivary glands

Type of trial	Enrolled patients	c-KIT expression by IHC	*KIT* or *PDFRA* mutations	Imatinib dose	Results	Reference
Multicentre single arm, two stage phase II clinical trial	Patients (N=16) with unresectable or metastatic AdCC	Present	NP	400 mg×2 daily	No evidence of objective response in 15 assessable patients. Early termination after completion of the first stage	Hotte et al, 2005[107]
Phase II study with combination of imatinib mesylate and cisplatin	N=14	Present	NP	800 mg as single agent; 400 mg in combination with cisplatin 80 mg/m²	Of the 12 assessable patients, 2 developed DP with imatinib as single agent and left the study; 1 had a documented PR; 4 had reduction in tumour size; the others showed SD (but short follow-up)	Slevin et al, 2004[108]
Pilot study	Patients (N=5) with metastatic AdCC	Present	No	400 mg×2 daily	DP in 2/5; DOD in 3/5.	Lin et al, 2005[105]
Phase II study for advanced AdCC of head and neck salivary glands	Patients (N= 10) with locally advanced or metastatic AdCC	Present	NP	400 mg (increased to 600 mg in 3 patients and to 800 mg in 1 patient)	2/10 patients with SD; 8/10 patients stopped the treatment after 2–14 months due to DP	Pfeffer et al, 2007[106]
Multicentre phase II trial	Patients (N=8) with recurrent or metastatic AdCC	Present	NP	400 mg×2 daily	Among the 6 assessable patients, 3 showed SD after 3 months of follow-up, one had a PR	Faivre et al, 2005[104]

DOD, death of disease; DP, disease progression; IHC, immunohistochemistry; NP, not performed; PR, partial response; SD, stable disease.

Take-home messages

- ▶ Adenoid cystic carcinomas (AdCCs) in salivary glands represent a very aggressive type of lesion, whereas breast adenoid cystic carcinoma shows a very good clinical behaviour, with an excellent 10-year prognosis.
- ▶ Breast AdCCs have a triple negative and basal-like phenotype; however they have a good long-term outcome.
- ▶ Breast and salivary gland AdCCs harbour the t(6;9)(q22—q24; p21—p23) recurrent translocation, involving the *MYB* and *NFIB* genes.
- ▶ At the present time, no specific targeted therapy is available for AdCC of either breast or salivary glands.

This fusion gene may provide new therapeutic avenues for the management of advanced AdCC; however, one must remember that targeting transcription factors is by no means a trivial task. Further functional studies investigating in greater depth the biological consequences of the *MYB* gain of function due to the *MYB-NFIB* fusion are eagerly awaited. Importantly, gene silencing experiments to demonstrate that *MYB* expression is selectively required for the survival of cancer cells with genetically activated *MYB* have yet to be performed.

CONCLUSIONS

As salivary and mammary glands are exocrine glands both showing a tubulo-acinar architecture, the remarkable similar morphological features observed in tumours arising in these two glandular structures should perhaps not come as a surprise.[110] A good example is offered by salivary duct carcinoma, a lesion that, at the morphological level, is remarkably similar to invasive ductal carcinomas of the breast,[92] and that can be categorised in the same molecular subtypes as those identified in invasive ductal breast carcinomas, namely luminal, HER2 and basal subtypes.[111]

AdCCs constitute an even better example of the similarities between the tumours affecting these sites. AdCCs of breast and salivary glands share a common pattern of growth, harbour an identical recurrent fusion gene (*MYB-NFIB*), and similar patterns of numerical chromosomal alterations. Surprisingly, however, despite these similarities, the behaviour of salivary gland and breast AdCCs differs: while salivary gland lesions have an aggressive behaviour and often metastasise, breast lesions have a much more indolent clinical course.

Although great strides have been made in the characterisation of these tumours, several questions remain unanswered. Do AdCCs constitute a tumour type with pluripotent patterns of evolution? And if so, what are the determinants of the distinct evolution/clinical behaviour? If overexpression of *MYB* and its target genes is the common denominator in the genesis of AdCCs regardless of the site of origin, what then makes their behaviour differ in salivary gland and breast? It would be plausible that different tumour-microenvironment interactions may account for the different metastatic proclivity of breast and salivary gland AdCCs; alternatively, it could be that the *MYB-NFIB* translocation may have similar impacts on the morphology of the tumour in different sites, but different effects on the metastatic ability dependent on the target epithelial cell (ie, cell of origin). With the advent of massively parallel sequencing and the opportunity to characterise the genome and transcriptome from these cancers, new opportunities to define the molecular determinants of the behaviour of these fascinating lesions will emerge.[112 113]

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