Head and Neck Pathol
DOI 10.1007/s12105-015-0645-x

ORIGINAL PAPER

Clinicopathologic and Immunophenotypic Characterization of 25 Cases of Acinic Cell Carcinoma with High-Grade Transformation

Lester D. Thompson[1] · Muhammad N. Aslam[2] · Jennifer N. Stall[2] · Aaron M. Udager[2] · Simion Chiosea[3] · Jonathan B. McHugh[2]

Received: 10 July 2015 / Accepted: 3 August 2015

Abstract Acinic cell carcinoma (AiCC) with high-grade transformation is a rare variant of AiCC composed of both a conventional low-grade (LG) AiCC and a separate high-grade (HG) component. We describe here, the clinicopathologic and immunohistochemical features of 25 cases diagnosed between 1990 and 2015. Available tissue was analyzed and compared with a cohort of pure LG AiCC for the morphologic and immunophenotypic profile. Incidence was higher in females (1.8:1) than males with an overall mean age at presentation of 63.2 years. All tumors occurred in the parotid gland including 76 % with facial nerve trunk and branches involvement. Most patients were treated with extensive resection and adjuvant therapy. Local recurrence or distant metastasis occurred in most patients, with 72.7 % dead with disease (mean 2.9 years) and 3 patients alive with disease (mean 2.4 years). The majority of the tumors were composed of a LG microcystic AiCC and a HG component consisting of invasive lobules of undifferentiated cells with predominantly solid, cribriform, and glandular patterns. Acinic differentiation was still present in HG areas but aggressive features such as perineural invasion (76 %), lymphovascular invasion (62 %), positive margins (72 %), high mitotic rate, atypical mitoses and/or comedonecrosis (86 %) were easily identified. Compared to the pure LG AiCC, the cases with HG transformation showed significantly increased expression of cyclin-D1, p53 and Ki-67. Most HG areas of AiCC expressed membranous β-catenin (92 %) and were negative for p63 (three cases were focally positive), S100, SMA, androgen, and estrogen receptors. DOG1 expression was present in all LG AiCC tested with retained expression in 91 % of cases with HG transformation, supporting acinic differentiation in the HG foci. Recognition of AiCC with high-grade transformation is imperative as more aggressive clinical management is warranted.

Keywords Acinic cell carcinoma · High-grade transformation · Dedifferentiated · Salivary gland · DOG1

Introduction

Acinic cell carcinoma (AiCC) is an uncommon carcinoma of major and minor salivary glands, accounting for approximately 6–7 % of all salivary gland neoplasms [1, 2]. The vast majority (90 %) of AiCCs arise in the parotid gland. Serous acinar cell differentiation, which is characterized by cytoplasmic zymogen secretory granules is a diagnostic feature of AiCC. Some AiCC also have clear, oncocytic and vacuolated cells. A variety of growth patterns can be appreciated in AiCC including solid, microcystic, follicular, and papillocystic. AiCC are typically

Preliminary findings presented at the Annual Meeting of the United States and Canadian Academy of Pathology, Vancouver, BC, Canada, March, 2012.

✉ Jonathan B. McHugh
jonamch@umich.edu

[1] Department of Pathology, Southern California Permanente Medical Group, Woodland Hills Medical Center, Woodland Hills, CA, USA

[2] Department of Pathology, University of Michigan Health System, 2G332 UH, 1500 E. Medical Center Drive, Ann Arbor, MI 48109, USA

[3] Department of Pathology, University of Pittsburgh Medical Center, Presbyterian University Hospital, Pittsburgh, PA, USA

Published online: 06 August 2015

cytologically low grade without atypia, increased mitoses, and necrosis. Cases with high-grade transformation (also referred to as dedifferentiation) are exceedingly rare and are defined as being composed of a conventional low-grade (LG) and a morphologically transformed high-grade (HG) component, which may consist of high-grade adenocarcinoma, poorly-differentiated carcinoma, small cell carcinoma, or undifferentiated carcinoma. High-grade transformation in AiCC can progress from any conventional AiCC pattern to a high-grade carcinoma typically lacking acinic differentiation supporting the concept of "dedifferentiation" [3]. AiCC with high-grade transformation has a more aggressive clinical course than conventional AiCC, and therefore, it is important for surgical pathologists to recognize this entity.

Stanley et al. [3] published the first series of six cases of AiCC with high-grade transformation in 1988, describing the characteristic dimorphic histopathology of these tumors and recognized their aggressive clinical behavior. Since the initial case series, several other case reports and small series have been published [4–14]; all report that compared to the classical AiCC, AiCC with high-grade transformation presents in an older age group, shows a slight female predominance and advanced local disease. These tumors often involve the facial nerve and have a high tendency to recur, metastasize, and have a poor prognosis. Less than fifty cases have been described, but all of them have a parotid gland primary [4].

Two previous reports have described the phenotype of the high-grade component of these tumors. The first, a case report by Piana et al. [7], showed morphologic and immunophenotypic features of myoepithelial differentiation, demonstrating diffuse S100 protein expression with focal smooth muscle actin and cytokeratin expression. Later, in 2009, a series of nine cases by Skálová et al. [11], further characterized the high-grade component as strongly expressing membrane cytokeratin 18 and β-catenin as well as nuclear cyclin-D1. In contrast to Piana et al., they observed loss of S100 protein within the regions of high-grade transformation as well as loss of enzymatic markers, α-1-antitrypsin and lysozyme. Both components of the tumors lacked staining or overexpression for Her-2/neu, androgen receptor, c-KIT, and epidermal growth factor receptor. Overexpression of p53 has been an inconsistent feature in the HG areas of AiCC [4] but some observed a higher expression of p53 in the transformed areas than in the conventional AiCC [11, 15]. To further study the morphologic and immunophenotypic features of AiCC with high-grade transformation, we performed a multi-institutional clinicopathologic review of our experience of AiCC with high-grade transformation in order to better understand these rare salivary gland carcinomas.

Materials and Methods

Following Institutional Review Board (University of Michigan, Southern California Permanente Medical Group, University of Pittsburgh Medical Center) approval, we performed a retrospective review of departmental cases and institutional medical records from 1990 through 2015 to identify cases. Inclusion criteria included cases in which there was evidence of a classical low-grade AiCC as well as a morphologically distinct high-grade component. Specifically, the high-grade component was distinct from the low-grade component and characterized by a combination of atypical histologic features including increased mitotic rate, cytologic atypia and pleomorphism, and necrosis. Similar to some other authors, we did not exclude cases that fit these criteria but retained acinic differentiation [5, 8]. Original slides of high-grade salivary gland carcinomas were reviewed to identify cases with an unrecognized AiCC component. The de-identified clinicopathologic data of patients with high-grade transformation of AiCC were reviewed to evaluate demographic data (age, sex), clinicopathologic features (clinical presentation, size of lesion, cranial nerve VII involvement, margin status, perineural invasion, lymphovascular invasion, lymph node involvement), and treatment with follow-up, including recurrence, distant metastases and disease status at the time of last follow-up. Recurrence was defined as clinically and/or histologically documented tumor recurrence. Four cases were evaluated as biopsy only samples, and thus certain staging features as well as histologic features could not be reliably assessed. To further define the morphologic spectrum of AiCC with high-grade transformation, the following histomorphologic features were evaluated: LG component, HG component growth pattern and architecture, presence of acinic differentiation in HG areas (focal = rare acinic cells vs. prominent = easily identified acinic cells in each hpf), cellular pleomorphism and atypia, mitotic activity, atypical mitoses, presence or absence of necrosis (and type), perineural invasion and lymphovascular invasion. Mitotic rates were defined as follows: low <2 mitoses/10 hpf, intermediate 2–5 mitoses/10 hpf, and high >5 mitoses/10 hpf. When sufficient histologic material was available, the immunophenotypic spectrum was evaluated by staining sections from paraffin-embedded tissue blocks with the following antibodies at optimized dilutions: CK5/6 (clone D5/16B4, 1:500, Ventana Medical Systems), CAM 5.2 (clone CAM5.2, 1:40, BD Bioscience), S100 protein (rabbit polyclonal, 1:400, Ventana Medical Systems), smooth muscle actin (SMA)(clone 1A4, 1:2000, Ventana Medical Systems), p63 (clone 4A4, 1:400, Ventana Medical Systems), β-catenin (clone 14, 1:500, Ventana Medical Systems), cyclin-D1 (clone SP4, 1:100, Cell

Marque Corp), Ki-67 (clone 30-9, 1:200, Ventana Medical Systems), p53 (clone D)-7, 1:100, Ventana Medical Systems), androgen receptor (AR) (clone SP107, 1:50, Cell Marque), estrogen receptor (clone SP1, prediluted, Ventana Medical Systems), Her-2/neu (clone 4B5, prediluted, Ventana Medical Systems), and DOG1 (clone SP31, 1:50, Cell Marque Corp). Comparison to five cases of conventional LG AiCC without HG transformation was also performed. Presence/absence of staining in LG and HG areas was assessed as well as percentage of staining in regions of high-grade transformation for cell cycle markers (cyclin-D1, p53, Ki-67). Her2/neu overexpression was classified on a 0–3+ scale based on well established and previously described criteria. Luminal DOG1 staining was considered positive and was assessed as a percentage of the respective (LG vs. HG) component being analyzed.

Results

Twenty-five cases of AiCC with high-grade transformation were identified. The clinical and demographic characteristics of these cases are summarized in Table 1. Tumors occurred with a female sex predilection (16 women: 9 men) between the ages of 42–88 years (mean 63.2 years). All tumors developed in the parotid gland, ranging from 1.8 to 9.5 cm (mean 3.9 cm) with 16 of 21 assessed patients demonstrating facial nerve (main trunk and/or branches) involvement at presentation. Almost all patients were managed with a total parotidectomy (n = 24), along with a selected or radical lymph node dissection (n = 12); one patient was inoperable and thus had a biopsy only. Adjuvant therapy (n = 16) including radiation and various chemotherapy regimens were used to manage the primary tumors or as part of treatment for recurrence. Thirteen of 18 resection samples available for review showed positive margins. The mean follow-up was 3.3 years, with only 3 patients lost to follow-up. Three patients are alive with no evidence of disease (mean 7.3 years), 2 of which were managed with additional radiation therapy only. Three patients are alive with disease (mean 2.4 years), two of which were managed with radiation and chemotherapy. All of the remaining patients were dead with disease (mean 2.9 years), with a range of 1 month to 10.7 years. There was no detectable impact on outcome based on the type of surgery or adjuvant therapy employed. Patients presented with recurrent disease (local or metastatic) 3–38 months after initial treatment, with an average of 16.1 months to first recurrence.

The typical gross appearance of conventional LG AiCC differed from those AiCC with HG transformation as seen in Fig. 1. LG AiCC's (Fig. 1a) were comprised of circumscribed, tan, soft fleshy nodules. AiCC with HG transformation had areas that resembled LG AiCC but had a more infiltrative appearance (Fig. 1b). Foci of yellow degeneration or necrosis were present in all AiCC with HG transformation.

Table 1 Demographics of acinic cell carcinoma cases with high-grade transformation

Feature	N = 25
Gender	
Females	16
Males	9
Age at presentation (years)	
Mean	63.2
Median	66.0
Range	42–88
Clinical presentation[a]	
Mass	13
Pain	4
Length of time with symptoms (mo)[a]	
Mean	11.1
Range	1–36
Location: parotid gland	25
Size (cm)	
Mean	3.9
Range	1.8–9.5
Patients with lymph node metastases[a]	10
Stage	
I	3
II	5
III	4
IVA–IVC	13
Follow-up status	
Alive with no evidence of disease (mean years)	3 (7.3)
Alive with disease (mean years)	3 (2.4)
Dead with disease (mean years)	16 (2.9)
Lost to follow-up	3

[a] Parameter not reported for all patients due to consultation type cases

Histopathologic features of the cases of AiCC with high-grade transformation are summarized in Table 2 and Figs. 2, 3. Most tumors contained a LG component with a microcystic growth pattern (range 5–90 % of the total tumor volume); most of these LG microcystic areas were also associated with a prominent lymphoid stroma (Fig. 2). A quarter of tumors also contained a LG solid component (range 5–20 %) mixed with the microcystic component. All cases except one contained a HG component consisting predominantly of invasive lobules of undifferentiated cells with areas of acinic differentiation. In most of these cases, acinic differentiation was easy to identify with only 3 cases with rare foci of acinic differentiation. Solid growth was

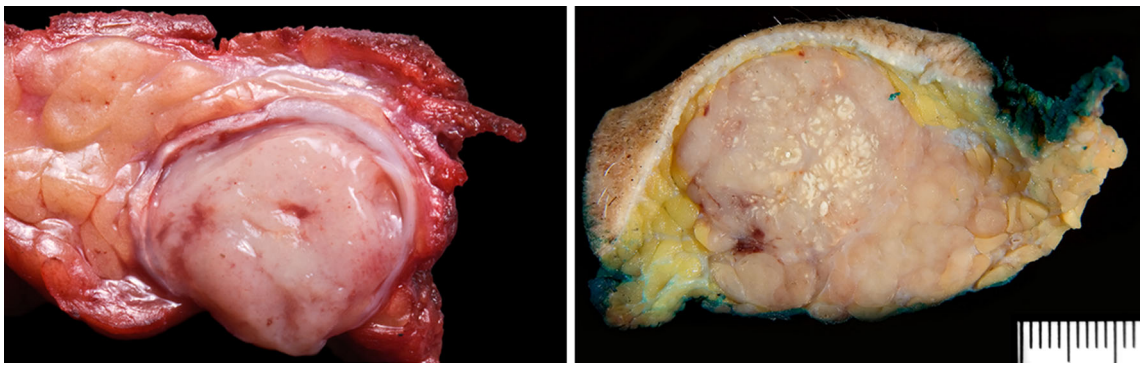

Fig. 1 Macroscopic photograph of the excised tumor specimens from a conventional pure low-grade acinic cell carcinoma (AiCC) (*left*) and AiCC with high-grade transformation (*right*). The pure low-grade neoplasm is a well-circumscribed solid, fleshy, tan nodule with a thick fibrous capsule. In contrast, AiCC with high-grade transformation tend to be more infiltrative and often show of comedonecrosis

present in most of the tumors (n = 20), with trabecular (n = 10), cribriform (n = 6), cystic (n = 5), and single cell infiltrative growth (n = 3) present in some cases. One unusual case had salivary duct-like growth without acinic differentiation and AR negative. Rare areas of small cell and large cell cytology were present in 25 and 25 % of cases, respectively, showing a "neuroendocrine" type appearance. Nuclei were typically moderately-sized with prominent nucleoli and moderate to marked atypia. Perineural invasion (16/21), intermediate to high mitotic rate with atypical mitoses (21/22) and necrosis, typically comedonecrosis (19/22) were seen in most cases.

Immunohistochemical features of AiCC with high-grade transformation compared to cases of pure LG AiCC are presented in Table 3 and Fig. 4. CK 5/6 (high molecular weight keratin) was observed focally in 33 % of cases with high-grade transformation, while 95 % of tumors with HG AiCC retained strong expression of CAM 5.2 (low molecular weight keratin). These results were similar to the pure LG AiCC tumors. All studied HG areas expressed diffuse membranous β-catenin and were negative for SMA, AR, and ER and 11 % had rare foci of S100 staining. Three of 15 (20 %) cases with HG transformation expressed p63 but it was weak and focal only. Her-2/neu overexpression (3+) was present in only two cases (17 %) but an additional six cases had 2+ Her-2/neu expression. Compared to pure LG AiCC cases, AiCC with HG transformation were significantly more likely to have 2+ or 3+ Her-2/neu expression ($p < 0.05$, Chi squared test). Not surprisingly, the HG component in transformed cases demonstrated increased expression of cell regulatory markers cyclin-D1 and Ki-67, as compared to conventional LG AiCC ($p < 0.05$, Student's *t* test). Similarly, p53 immunoreactivity was greater in transformed cases as compared to pure LG AiCC ($p < 0.05$, Student's *t* test). Overall, five cases (33 %) demonstrated moderate to strong, diffuse p53 staining in the HG AiCC component; in addition, one case (7 %) showed complete

Table 2 Histopathologic features of acinic cell carcinoma cases with high-grade transformation

Feature	Number
Low grade component	
Microcystic	19
Range of low grade tumor volume	5–90 %
Acinic differentiation in high-grade areas	
Prominent	19
Focal	3
Growth pattern/architecture	
Solid	20
Trabecular	10
Cribriform	6
Cystic	5
Cellular pleomorphism	
Moderate	12
Severe	10
Mitotic activity	
Low	1
Intermediate	10
High	11
Necrosis	
Present (comedonecrosis)	19
Absent	3
Margins[a]	
Positive	13
Negative	5
Perineural invasion[a]	
Present	16
Absent	5
Lymphovascular invasion[a]	
Present	13
Absent	8

[a] Four of the cases were biopsy samples only, and thus certain histologic features could not be reliably assessed

loss of p53 staining in the HG AiCC (with appropriate internal positive controls). Luminal DOG1 expression was similar in LG and HG areas of AiCC with HG transformation averaging 69 % in the LG areas as compared to 56 % in the HG areas. Smooth muscle actin was negative in all cases which, coupled with the rare p63 and CK5/6 expression and negative S100 staining, argue against any evidence of myoepithelial differentiation.

Discussion

First described in 1892 by Nasse [16], AiCC were originally referred to as "acinic cell tumors" due to the uncertainty about their clinical behavior. A little more than 60 years later, Buxton et al. [17] and Foote Jr. and Frazell [18] first described the malignant potential of AiCC, and in 1988, nearly 100 years from original description, Stanley et al. [3] reported the first cases of AiCC with dedifferentiation, also known as high-grade transformation. While the clinicopathologic findings of classic AiCC are well documented, less than fifty cases of AiCC with HG transformation are documented in the literature. This cohort of 25 cases (a subset were previously reported in a re-evaluation of AiCCs after the discovery of mammary analogue secretory carcinoma [14]) documents additional morphologic and immunophenotypic features of these tumors and expands the overall outcome data.

The epidemiologic and clinical findings of our cohort are similar to those previously observed. AiCC with HG transformation occurs in older patients (mean 63 years) as compared to conventional AiCC (mean 44 years) [1]. Prior studies have shown a slight female predominance [4, 14], with a 1.8:1 ratio of females to males in our cohort. As with prior reports, all our cases arose in the parotid gland, typically with a rapid clinical onset and often with symptoms of facial nerve involvement (76 % of cases in our cohort). All patients were treated with surgery, often including lymph node dissection, with many further managed with adjuvant therapy. In spite of aggressive therapy, 86 % of

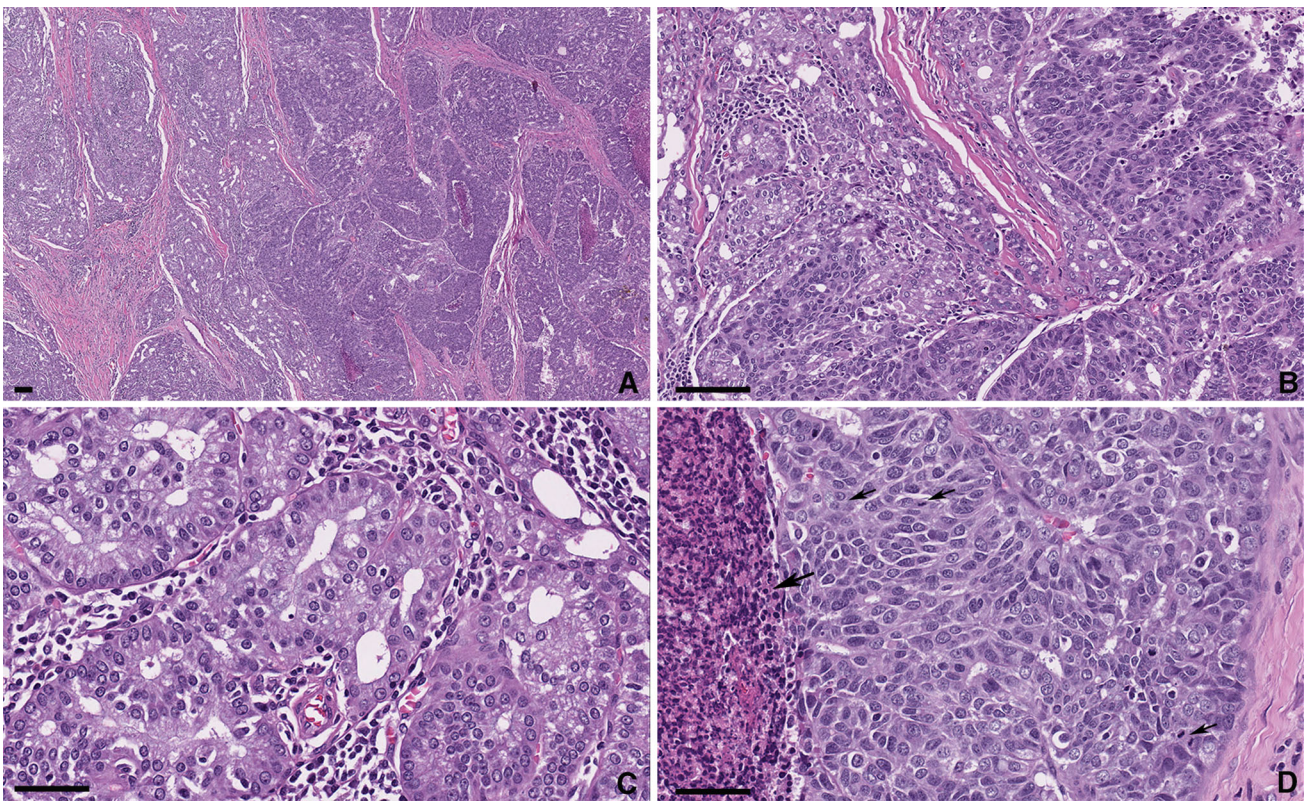

Fig. 2 Histopathologic features of AiCC cases with high-grade transformation. **a** Cases of AiCC with high-grade transformation are composed of a low-grade AiCC (*left half*) and a distinct high-grade component (*right half*). **b** The low-grade component is well-defined from the areas with high-grade transformation and displays microcystic differentiation with background lymphoid stroma, a feature seen in all twelve cases in this study. **c** Prominent acinic cells are scattered throughout the tumor in the low-grade component. **d** High-grade foci demonstrate marked cytologic atypia with frequent foci of comedonecrosis (*left*). *Bar* 100 μm (**a**, **b**) 50 μm (**c**, **d**)

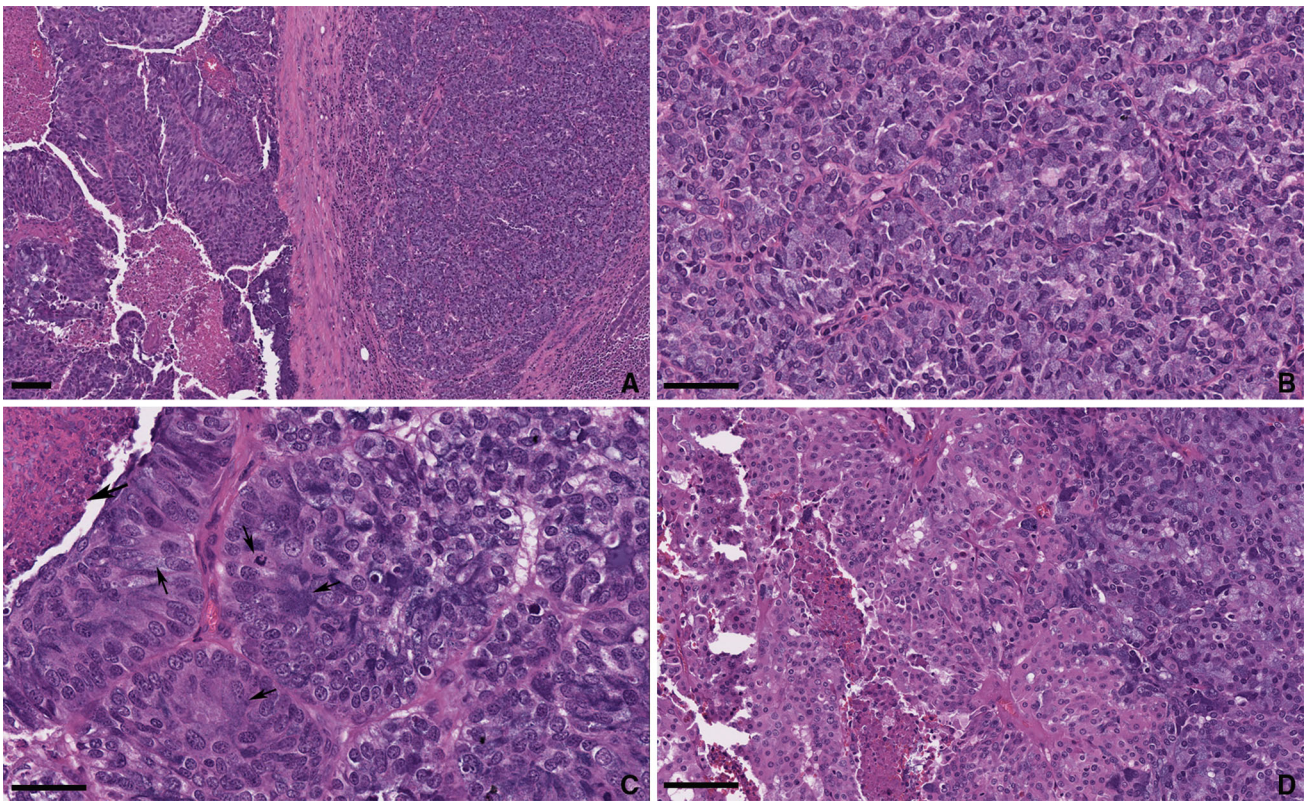

Fig. 3 Histopathologic features of AiCC cases with high-grade transformation. **a** Some cases of AiCC with high-grade transformation (*left*) were composed of a low-grade solid AiCC component (*right*). Extensive comedonecrosis can be seen at low-power magnification. **b** The low-grade component is comprised of solid sheets of acinic cells with numerous zymogen granules. **c** In our series, over 90 % of AiCC with high-grade transformation had easily recognizable acinic differentiation. **d** Whereas most cases with high-grade histology were identical, one case of AiCC with high-grade transformation had focal areas with oncocytic differentiation and one case resembled salivary duct carcinoma, however, this case was negative for androgen receptor. *Solid bar* 100 μm (**a**, **d**) 50 μm (**b**, **c**)

patients recur with an overall median survival of 2.2 years (mean 3.3 years), slightly less than the 4.3 years median survival reported by Skálová et al. [11].

The histologic findings in this cohort are similar to those previously reported with the low-grade component often being microcystic (sometimes solid) with abundant lymphoid stroma. Not surprisingly, the high-grade component in our cohort, as with other reports, was comprised of large invasive lobules with cells demonstrating increased pleomorphism, increased mitoses and frequent necrosis, often of the comedo-type. In contrast to Skálová et al. and other authors, the high-grade component in most of our cases contained scattered cells with prominent acinic cell differentiation. These cells were easily identified in most cases. This finding suggests the ability to diagnose a HG transformation of AiCC in small biopsy or core needle cases, and further supports the preferred term of HG transformation instead of dedifferentiation.

While the clinical and histologic findings of our cohort are quite similar to those previously reported, the immunophenotypic findings differ. In contrast to the case described by Piana et al. [7], none of our cases expressed myoepithelial differentiation; nearly all of our cases lacked expression of CK5/6, p63, S100 and SMA, which is similar to that seen in the series reported by Skálová et al. The cases with CK5/6 and p63 expression only had rare foci, often with weak staining. Also similar to the series described by Skálová et al., all our cases demonstrated diffuse strong membranous β-catenin and lacked AR expression. Interestingly, the pure LG AiCC cases in our series also demonstrated diffuse strong membranous β-catenin expression, which differs from that previously seen by Skálová et al. In addition to a high Ki-67 index, we also saw elevated expression of cyclin-D1, which correlates with increased proliferation observed in these high-grade tumors.

Our immunohistochemical evaluation also confirmed an increased immunoreactivity of p53 in HG transformed AiCC cases as compared to pure LG AiCC [11, 15]. Previous studies have demonstrated high concordance between p53 immunohistochemistry pattern and *TP53* mutation status by sequencing. For example, Yemelyanova et al.

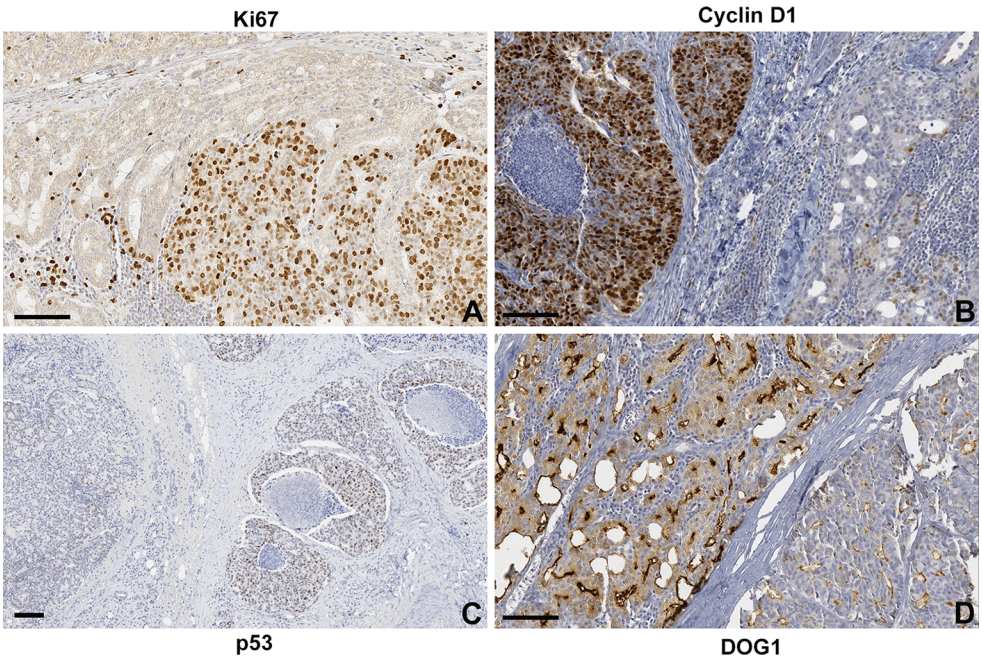

Fig. 4 Representative immunohistochemical staining for Ki67 (**a**), cyclin-D1 (**b**), p53 (**c**) and DOG1 (**d**) comparing staining in low-grade and high-grade regions of tumor. Ki-67, cyclin-D1 and p53 were significantly more expressed in the high-grade regions of AiCC with high-grade transformation as compared to the low-grade foci. Variable expression of DOG1 was seen throughout the cases and was present in all low-grade foci and was retained in over 90 % of high-grade foci. *Bar* 100 μm (**a**, **b**, **c**, **d**)

Table 3 Immunohistochemical features of acinic cell carcinoma cases with high-grade transformation

Antibody	# (% positive)	Location and quality
CK5/6	4/12 (33 %)	Focal, cytoplasmic
CAM5.2	18/19 (95 %)	Cytoplasmic and membranous
DOG-1	8/13 (62 %)	Luminal staining only interpreted as positive; Cytoplasmic patchy and weak reactions were also seen (n = 3)
S100 protein	2/18 (11 %)	Nuclear only, focal
Cyclin-D1	13/14 (93 %)	Nuclear reaction, range of 5–90 %
p63	3/15 (20 %)	Focal, high grade component
p53	14/15 (93 %)	Nuclear, range of 10–90 %
SMA	0/13 (0 %)	
Androgen receptor	0/13 (0 %)	
Estrogen receptor	0/11 (0 %)	
β-catenin	14/14 (100 %)	Membranous (*not* nuclear)
Her-2/neu	2/12 (17 %)	3+ full circumferential
Ki-67	15/15 (100 %)	Range of 10–90 % of nuclei

Cyclin-D1, Ki-67 and p53 staining assessed in regions of high-grade transformation; HER-2/neu overexpression defined on a 0–3+ scale

[19] showed that 94 % of ovarian carcinomas with either clonal loss of p53 staining or moderate to strong, diffuse p53 expression have p53 mutations by DNA sequencing. Overall, in our cohort, 40 % of cases demonstrated either clonal p53 loss or moderate to strong, diffuse p53 staining in the HG AiCC component, suggesting that somatic alteration of *TP53* may play a role in the transformation of LG AiCC to HG carcinomas [20]. *DOG1* (also called FLJ10261 gene, *CCND1–EMS1* locus on chromosome 11q13; *GIST-1*), a calcium-activated chloride channel originally described in gastrointestinal stromal tumors, has been reported to be a marker of salivary acinar and

Table 4 Literature review of acinic cell carcinoma with high-grade transformation in combination with our cases [3, 5–15, 22–24]

Feature[a]	Our clinical series (N = 25)	Literature review (N = 40)	Our clinical series and reported cases (N = 65)
Gender			
Females	16	22	38
Males	9	16	25
Age at presentation (years)			
Mean	63.2	59.1	60.7
Median	66.0	61.5	62.0
Range	42–88	25–86	25–88
Clinical presentation			
Mass	13	40	53
Pain	4	8	12
Length of time with symptoms (mo)			
Mean	11.1	–	–
Range	1–36	–	–
Location: parotid gland	25	40	65
Size (in cm)			
Mean	3.9	3.8	3.9
Range	1.8–9.5	1.3–8	1.3–9.5
Patients with lymph node metastases	10	18	28
Stage			
I	3	3	6
II	5	11	16
III	4	6	10
IVA–IVC	13	19	32
Follow-up status			
Alive with no evidence of disease (mean months)	3 (87.2)	6 (35.3)	9 (26.0)
Alive with disease (mean months)	3 (28.4)	6 (30.0)	9 (20.8)
Dead with disease (mean months)	16 (34.6)	23 (46.1)	39 (38.4)
Lost to follow-up	3	5	8

[a] Clinical parameters were not reported for all cases (in our series or in the literature)

intercalated duct differentiation [21]. Similar to the twenty-eight classic AiCC cases described by Chênevert et al., all our cases of pure LG AiCC as well as most of the HG component of the transformed cases demonstrated luminal expression of DOG1, demonstrating the salivary acinar and intercalated duct origin of these tumors. Although luminal DOG1 expression was typical, some cases showed weak cytoplasmic staining. Similar to the morphologic presence of acinic differentiation, DOG1 expression was retained in the majority of AiCC with HG transformation. While a decreased expression of DOG1 was seen in a subset of AiCC with HG transformation, no difference or increase of expression was seen in others.

AiCC with HG transformation demonstrates an aggressive clinical course with frequent facial nerve involvement, metastases and death (Table 4) [3, 5–15, 22–24]. This appears to be a relatively uncommon and recently recognized phenomenon as several prior large studies fail to comment on this occurrence [25–27]. While no definitive immunophenotypic profile could be determined from this small cohort, the increased cyclin-D1, p53, and Ki-67 are consistent with a more aggressive neoplasm. We did not demonstrate myoepithelial differentiation and showed, in contrast to others, a retained morphologic acinic differentiation and DOG1 expression in the HG areas of AiCC with HG transformation. These latter features aid in making the diagnosis of AiCC with HG transformation and support use of the term HG transformation as opposed to dedifferentiated. Although some AiCC with HG transformation may resemble salivary duct carcinoma, the lack of apocrine

differentiation, the presence of acinic differentiation, negative AR and DOG1 expression argue against this possibility. Ultimately, recognition of AiCC with high-grade transformation is important for surgical pathologists as more aggressive clinical management is warranted. Further studies with larger sample size or potentially molecular sequencing will be needed to uncover the key genetic drivers in these aggressive tumors.

Compliance with Ethical Standards

Conflict of interest None.

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