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ANATOMICAL PATHOLOGY

CD117 and CD43 are useful adjuncts in the distinction of adenoid cystic carcinoma from adenoid basal cell carcinoma

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Summary

Distinction of cutaneous adenoid cystic carcinoma (ACC) from adenoid basal cell carcinoma (BCC) is an occasional diagnostic dilemma in dermatopathology. We examined the immunohistochemical staining patterns with CD117 and CD43 in ACCs and BCCs, including BCCs with an adenoid growth pattern, to determine whether a combination of these markers can assist in the differential diagnosis. Fifteen cases each of ACC and BCC, including seven BCCs with a partial or entirely adenoid growth pattern were immunohistochemically stained for CD117 and CD43. The stains were interpreted semi-quantitatively. Staining for CD43 and CD117 was significantly more common in ACC than in BCC. Forty percent of ACCs showed staining for CD43, while no cases of BCC were positive. CD117 was positive in all cases of ACC, with 93% showing moderate or strong staining. BCC were less frequently positive, with only 20% of cases showing labelling of weak or moderate intensity. Immunohistochemical positivity for CD117 and CD43 are likely to be helpful adjuncts in the separation of cutaneous ACC from adenoid BCC.

Key words: Adenoid cystic carcinoma, basal cell carcinoma, CD117, CD43, dermatopathology.

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INTRODUCTION

The morphological distinction of cutaneous adenexal tumours from basal cell carcinoma (BCC) is a frequent diagnostic challenge in dermatopathology. This differential has many guises, one of which is separating cutaneous adenoid cystic carcinoma (ACC) from BCC, particularly those with an 'adenoid' growth pattern.

Cutaneous ACC is histologically identical to its more common salivary gland counterpart. ACC is characterised by cribriform and less often tubular or solid formations of admixed epithelial and myoepithelial cells. The latter are typically numerous and their round to angular nuclei, scant cytoplasm and indistinct cytoplasmic borders impart a basaloid appearance. These cells surround the punched out pseudoglandular spaces of the characteristic cribriform structures, which contain either eosinophilic basement-membrane like material or basophilic ground substance. Occasional 'true' glands, containing eosinophilic secretory products, are lined by low cuboidal epithelial cells with eosinophilic cytoplasm. Cutaneous ACC, like those of the salivary gland and elsewhere, share a propensity for perineural invasion.[1,2]

Basal cell carcinomas are the most common cutaneous malignancy. They are characterised by islands and nests of hyperchromatic basaloid cells with scant, ill-defined pale cytoplasm. In the adenoid variant the tumour islands have a reticulated pattern, resulting in rounded collections of basophilic ground substance, mimicking ACC.[3]

Histological clues to separate these entities include peripheral palisading of tumour cells, stromal retraction around invasive tumour islands and epidermal attachment, which are features of BCCs not shared with cutaneous ACC. Previous studies have found that staining for EMA, CAM5.2, S100 and CEA is generally positive in ACC but negative in BCC.[2,3]

The distinction is important. Following complete excision up to 50% of cutaneous ACC may recur.[1] In a recent series three of 18 exhibited metastatic potential.[1] This contrasts with BCC where, in the absence of aggressive phenotype, perineural invasion and/or involved margins, the outlook following complete excision is excellent, with a low risk of local recurrence and a negligible risk of metastasis.[3]

We investigated whether markers considered specific for ACC, including CD117 and CD43 could be of value in distinguishing ACC from adenoid BCC.

MATERIALS AND METHODS

The pathology archives of PathWest Laboratory Medicine at QEII site were searched for cases of ACC arising at any site and of BCC with a description of adenoid features between the years 1997 and 2014. BCC numbers were supplemented with unselected routine BCC cases. All slides were reviewed by a dermatopathologist (BAW) to confirm the diagnoses. Clinical data were obtained from pathology request forms.

Immunohistochemical (IHC) analyses were then performed on additional 4–6 μm sections mounted on positively charged slides from each case on the Ventana BenchmarkXT automated staining machine (Ventana Medical Systems, USA). The processor deparaffinised the slides, carried out antigen retrieval utilising the on-board CCI retrieval solution, and incubated the slides in primary antibody. CD117 (T959 clone, dilution 1:100; Leica Biosystems, Germany) was incubated for 40 min at room temperature with on-board amplification and CD43 (DFT-1 clone, dilution 1:50; Dako, Denmark) was incubated for 32 min at 36°C. Visualisation was by the on-board ultraview DAB detection kit. Sections were then counterstained with haematoxylin to provide nuclear detail.

IHC staining for CD117 and CD43 was scored semi-quantitatively by estimating percentage tumour cell positivity as: 0, no tumour cell staining; 1+, 0–5% tumour cells staining; 2+, 6–49% cell staining; and 3+, >50% cell staining.

RESULTS

Clinical features

Fifteen ACCs were identified. The patient age ranged from 19 to 81. Two primary cutaneous forehead ACCs were identified.

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Another dermal ACC was identified, however it was unclear whether this represented a primary cutaneous ACC or a metastatic tumour deposit. Six cases arose within major salivary glands, five had origin in minor salivary glands and one was a metastatic ACC to the liver (Table 1).

Fifteen BCCs were identified. The patient age ranged from 40–86. Eleven cases were on the head and/or neck, two were on the trunk and two were from the upper limb (Table 2).

Histological features

All cases of ACC showed areas of classic morphology with at least partial cribriform growth containing alternating basophilic and eosinophilic material within the cribriform spaces and comprising a biphasic cell population (Fig. 1). All examples were of low grade, without significant mitotic activity, necrosis, areas of solid growth or dedifferentiation.

Seven of the 15 BCCs exhibited complete or partial adenoid growth, characterised by nodules of basaloid cells with a cribriform growth pattern and rounded spaces containing basophilic material (Fig. 2). Where other growth patterns were encountered they included nodular, nodular-cystic, superficial and infiltrating. The remaining eight BCCs exhibited superficial (two cases), mixed superficial and nodular, mixed nodular and infiltrating (three cases), purely infiltrating and purely nodular-cystic growth.

Immunohistochemistry

Membrane staining with or without a cytoplasmic blush was considered positive for both CD117 and CD43.

Positive staining for CD117 was at least focally observed in all cases of ACC, with semiquantitative scores ranging from 1+ to 3+ (Table 1). In 10 of the 15 cases this staining was extensive, with more than 50% of tumour cells positive (Fig. 3A). In contrast, only three BCCs exhibited CD117 membrane positivity and in all cases staining was focal (Fig. 3B). Care was taken not to count scattered positively stained melanocytes enmeshed within the lesional basaloid cells (Fig. 3C, inset). The sensitivity of CD117 for ACC was 100%, with a specificity of 80%.

CD43 staining was focally observed in six of the 15 ACCs (Fig. 3C), with semiquantitative scores ranging from 0 to 2+ (Table 2). None of the BCCs exhibited any positivity for CD43 (Fig. 3D). The specificity of CD43 for ACC was 100%, with a sensitivity of 40%.

Table 1 Adenoid cystic carcinoma: clinical features and immunohistochemical staining results

Case no.	Age	Site	CD117 staining	CD43 staining
1	53	Forehead	2+	0
2	56	Scalp	3+	2+
3	77	Right submandibular	3+	0
4	61	Endobronchial tumour	3+	1+
5	67	Left minor salivary gland	2+	2+
6	56	Maxilla	2+	1+
7	38	Metastatic deposit in liver	3+	0
8	34	Right parotid gland	3+	0
9	64	Right submandibular gland	3+	2+
10	19	Left parotid gland	3+	0
11	81	Left submandibular gland	3+	1+
12	66	Left submandibular gland	1+	0
13	43	Left endobronchial	3+	0
14	43	Umbilicus (primary/metastasis)	2+	0
15	61	Larynx	3+	0

Table 2 Basal cell carcinoma: clinical features, histomorphology and immunohistochemical staining results

Case no.	Age	Site	Growth patterns	CD117 staining	CD43 staining
16	81	Right temple	Adenoid, nodular & superficial	0	0
17	68	Posterior neck	Adenoid & infiltrating	0	0
18	87	Right post-auricular	Adenoid & nodular-cystic	0	0
19	59	Posterior neck	Adenoid	0	0
20	83	Left upper lip	Adenoid & nodular-cystic	1+	0
21	57	Right temple	Adenoid & nodular	0	0
22	63	Chest wall	Adenoid & nodular		
23	59	Left neck	Nodular	0	0
24	40	Right nasal bridge	Infiltrating	0	0
25	43	Left forehead	Nodular & superficial	0	0
26	47	Forehead	Nodular & infiltrating	0	0
27	86	Right forearm	Superficial	0	0
28	71	Left upper chest	Nodular-cystic	2+	0
29	79	Right shoulder	Superficial	0	0
30	82	Right ear	Nodular & infiltrating	1+	0

DISCUSSION

The morphological distinction of cutaneous ACC from BCC can be difficult and given its increased propensity for recurrence and metastasis, correctly identifying ACC is clinically important. Therefore, we investigated two newer antibodies considered relatively specific for ACC, to determine their utility in this distinction.

CD117 (also known as c-kit) is a transmembrane tyrosine kinase receptor, which upon activation initiates intracellular signals, ultimately resulting in cellular development and growth.[4,5] CD117 expression is observed in a range of normal cells, including melanocytes, and in neoplasms, including gastrointestinal stromal tumour, mast cell tumours, seminoma and ACC.[4,6] In the Mino *et al*. series of 66 ACCs and 98 other head and neck neoplasms, using two different CD117 clones, H300 (1:300 dilution; Santa Cruz Biotechnology, USA) and A4502 (1:100 dilution; Dako), almost all ACC exhibited positive cytoplasmic or membrane staining for either one or both CD117 clones.[7] In contrast, the morphologically similar

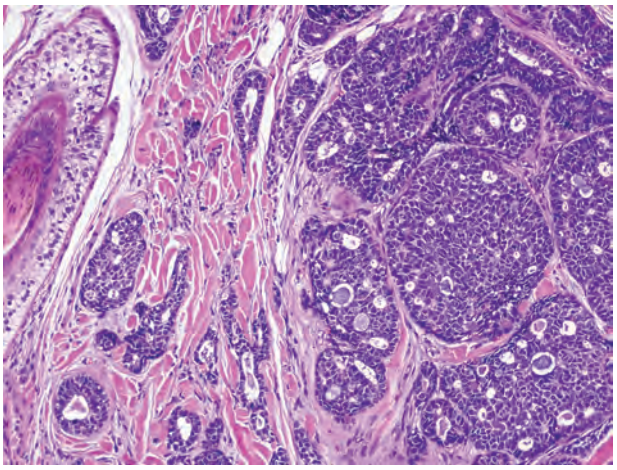

Fig. 1 Primary cutaneous adenoid cystic carcinoma (ACC) of the skin (Case 1) composed of bimorphic cells arranged in cribriform sheets punctuated by rounded spaces containing alternating basophilic and eosinophilic material (right) and tubular structures (central) (H&E).