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Morphologically low-grade spiradenocarcinoma: a clinicopathologic study of 19 cases with emphasis on outcome and MYB expression

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Spiradenocarcinoma is a rare skin adnexal neoplasm with potential for aggressive behavior, classified histologically into low- and high-grade tumors. Morphologically, low-grade tumors are thought to behave more favorably. Limited information is available, however, with only 18 published cases. To study their clinical behavior, histological features, and the diagnostic value of immunohistochemistry, 19 morphologically low-grade spiradenocarcinomas were retrieved and compared with 21 spiradenomas and cylindromas. H&E-stained sections were reviewed, follow-up was obtained, and immunohistochemistry for Ki-67, p53 and, MYB was performed. The tumors were solitary, measuring 0.8–7 cm (median: 2.7 cm), with a predilection for the head and neck of elderly patients (median age: 72 years; range 53–92) without gender bias. Histologically, the tumors were multinodular and located in deep dermis and subcutis. A pre-existing spiradenoma was present in all cases. The malignant component was characterized by expansile growth with loss of the dual cell population, up to moderate cytological atypia and increased mitotic activity (median: 10/10 HPF; range 1–28). Additional findings included squamoid differentiation ($n=9$), necrosis ($n=7$), and ulceration ($n=5$). P53 expression was variable and no significant differences were noted in the benign compared with the malignant parts of the tumors. In contrast, in the malignant components the Ki-67 proliferative index was slightly increased, and MYB expression was lost. Follow-up (median: 67 months; range: 13–132) available for 16 patients (84%) revealed a local recurrence rate of 19% but no metastases or disease-related mortality. In this large study with long-term follow-up, we demonstrate that spiradenocarcinomas with low-grade morphology pursue an indolent course, characterized by local recurrence only. Metastases and disease-related mortality appear to be exceptional. Lack of MYB expression may be useful as an additional aid in the diagnosis of these challenging tumors.
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Eccrine spiradenoma and dermal cylindroma are closely related tumors. They share many morphologic features, and occasionally hybrid tumors with spiradenomatous and cylindromatous components are encountered.[1,2] Although typically observed sporadically as solitary neoplasms, they may rarely be multiple in the setting of the Brooke–Spiegler syndrome.[3,4] Similar to adenoid cystic carcinoma of the breast and salivary glands, the *MYB-NFIB* gene fusion product, due to a t(6;9)(q22∼23; p23∼24) translocation, has recently been demonstrated in a subset of dermal cylindromas, resulting in overexpression of the MYB protein.[5–9] MYB is a leucine zipper transcription factor and has an important role in cell proliferation, apoptosis and cell differentiation.[10] It is downregulated in differentiated cells and highly expressed in immature, proliferating cells and may act as an oncogene in human cancer.[5,11–13]

Malignant transformation in eccrine spiradenoma, dermal cylindroma, and cylindroma-spiradenoma

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hybrid tumors is a rare event with only ~150 cases documented in the literature.[1,2,14] The malignant component shows a wide morphological spectrum, ranging from outright invasive adenocarcinoma to more innocuous appearances, reminiscent of basal cell adenocarcinoma of the salivary gland.[2] The tumors have therefore been separated histologically into morphologically low- and high-grade.[2,14] Their diagnosis depends entirely on adequate sampling and recognition of a pre-existing benign component, most commonly a benign spiradenoma. The morphologically low-grade malignant tumors pose a particular diagnostic challenge owing to their subtle histological changes, characterized by loss of a dual cell population, monotonous cellular growth, increased mitotic activity but only limited cytological atypia.[2,14] Although traditionally thought of as high-grade skin adnexal carcinomas with aggressive behavior and potential for metastatic spread and associated mortality, more recent studies have suggested a more indolent disease course with favorable outcome, at least for the morphologically low-grade tumors.[1,2,14,15] However, only 18 such cases have been reported with limited available follow-up. The aim of the present study was to study the outcome of morphologically low-grade malignant spiradenocarcinomas more comprehensively on a larger cohort with long-term follow-up. We also assessed the value of p53 and Ki-67 immunohistochemistry as an additional diagnostic aid in this setting and investigated MYB expression in these tumors in comparison with benign spiradenoma and cylindroma.

Materials and methods

Nineteen eccrine spiradenocarcinomas with low-grade morphological features, 10 eccrine spiradenomas, 10 dermal cylindromas, and one hybrid spiradenoma–cylindroma were retrieved from the surgical pathology files of the Departments of Pathology at NHS Lothian University Hospitals Trust, Edinburgh, UK, the University of Ljubljana, Ljubljana, Slovenia, the Clinical Hospital Center Sestre milosrdnice, Zagreb, Croatia, and referral files of one of the authors (TB).

Routine hematoxylin and eosin-stained sections were reviewed and immunohistochemistry was performed with antibodies to p53 (1:50 dilution; clone DO-7; Dako, UK, Cambridge UK), Ki-67 (1:100 dilution; clone MIB-1; Dako, UK, Cambridge UK) and MYB (1:300 dilution; clone EP769Y; Abcam, Cambridge, MA, USA). For MYB, pressure cooker antigen retrieval (0.001 M citrate buffer, pH 6.0) was performed prior to incubation with the primary antibody. Adenoid cystic carcinoma of salivary gland was used as a positive control.

Nuclear staining for Ki-67, p53, and MYB was scored and expressed as percentages of positive tumor cells after counting 10 high power fields (HPF). For p53 and MYB labeling the intensity of nuclear staining was expressed semiquantitatively as weak, moderate, or strong. Tumors expressing MYB in $<10\%$ of tumor cells were scored as negative.[5] The benign and malignant components of the morphologically low-grade spiradenocarcinomas were scored separately for p53, Ki-67, and MYB.

For statistical analysis the immunohistochemical expression data for Ki-67, p53, and MYB were analyzed using Graphpad Prism software. The non-parametric Mann–Whitney *U*-test was used to compare the benign to malignant aspects of the spiradenocarcinomas. All *P*-values are two-tailed with a 95% confidence interval.

Ethical approval was obtained from the Edinburgh Experimental Cancer Medicine Centre (ECMC SR223–10/S1402/33).

Results

Clinical Data

The clinical data are summarized in Table 1. The patients were elderly adults with a median age at presentation of 72 years (range: 53–92 years) and no significant gender bias. The anatomic distribution was wide. The majority of tumors ($n=10$) presented on the head and neck area with a predilection for the scalp ($n=5$) followed by the neck ($n=4$). One tumor presented in the external meatus of the ear. The second most frequently affected areas were the extremities ($n=5$) followed by the trunk ($n=4$). The tumors were large, with a median size of 2.7 cm

Table 1 Clinical information and follow-up

Case no.	*Sex/age*	*Site*	*Size (cm)*	*Follow-up*
1	F/71	Chest	2.5	N/A
2	F/92	Neck	4.0	NED, 25 m
3	M/60	Buttock	3.0	NED, 74 m
4	M/70	Scalp	1.1	Recurrence at 4 years; DUC; 120 m
5	F/89	Neck	1.5	DUC; 13 m
6	F/84	Scalp	1.5	Recurrence at 3 years; 84 m
7	F/59	Leg	4.0	NED, 60 m
8	F/67	Arm	0.8	Recurrence at 7 years; 132 m
9	M/74	Scalp	1.8	DUC; 50 m
10	M/76	Leg	7.0	NED, 36 m
11	M/83	Neck	7.0	DUC; 36 m
12	M/53	Scalp	2.0	NED, 42 m
13	F/60	Leg	2.8	NED, 132 m
14	M/68	Scalp	1.1	NED, 96 m
15	M/56	Back	1.5	NED, 132 m
16	F/87	External meatus ear	0.8	NED, 28 m
17	M/60	Chest	5.0	NED, 15 m
18	F/89	Neck	2.0	Recent case
19	F/73	Arm	1.2	Recent case

Abbreviations: DUC, death of unrelated cause; N/A, not available; NED, no evidence of disease.

(range: 0.8–7 cm). With the exception of one case, all tumors were solitary with the clinical appearance of a nodule (Figure 1) and less frequently a plaque or a papule. One patient with a presumed diagnosis of Brooke–Spiegler syndrome presented with seven additional benign dermal cylindromas and eccrine spiradenomas.

Histopathological Features

The tumors were based within the dermis with a multinodular growth pattern and well-demarcated outlines (Figure 2a and b). Additional involvement of subcutaneous adipose tissue was present in 17 cases. This feature could not be assessed in one tumor, and only one tumor was confined to the dermis.

All 19 tumors showed a spiradenocarcinoma with salivary gland-type basal cell adenocarcinoma-like pattern, low-grade morphology as recently described.[2] The malignant components showed loss of the dual cell population, and a diffuse growth of monotonous epithelial cells with mild to at most moderate cytological atypia characterized by enlarged vesicular nuclei with small nucleoli (Figure 3a and b). The cytoplasm was eosinophilic to clear and the nuclear-cytoplasmic ration was increased. Mitotic activity was readily identified with a median mitotic count of 10 mitoses/10 HPF (range, 1–28 mitoses/10 HPF) (Figure 4a). No atypical mitoses were noted. All tumors showed ductal differentiation (Figure 4b). Additional morphologic patterns included the presence of squamoid morules ($n=9$) and keratocysts ($n=7$) (Figure 4c). Tumor necrosis was identified in seven and epidermal ulceration was seen in five cases (Figure 4d). No perineural infiltration or lymphovascular invasion was present.

A benign counterpart was present in all cases, either as an eccrine spiradenoma in 18 cases or as a hybrid spiradenoma–cylindroma in one case. In 17 tumors the benign counterpart was only a minor component, representing between 5 and 40% (median: 10%) of the whole tumor. The pre-existing benign component was a major part of the tumor in two cases only with 70% and 90%, respectively. The benign counterpart was typically present at the edge of the tumor, either as a nodule or as a thin compressed rim. In 11 cases it merged with the malignant component, whereas it was present as a separate nodule in the remaining eight tumors (Figure 5a and b).

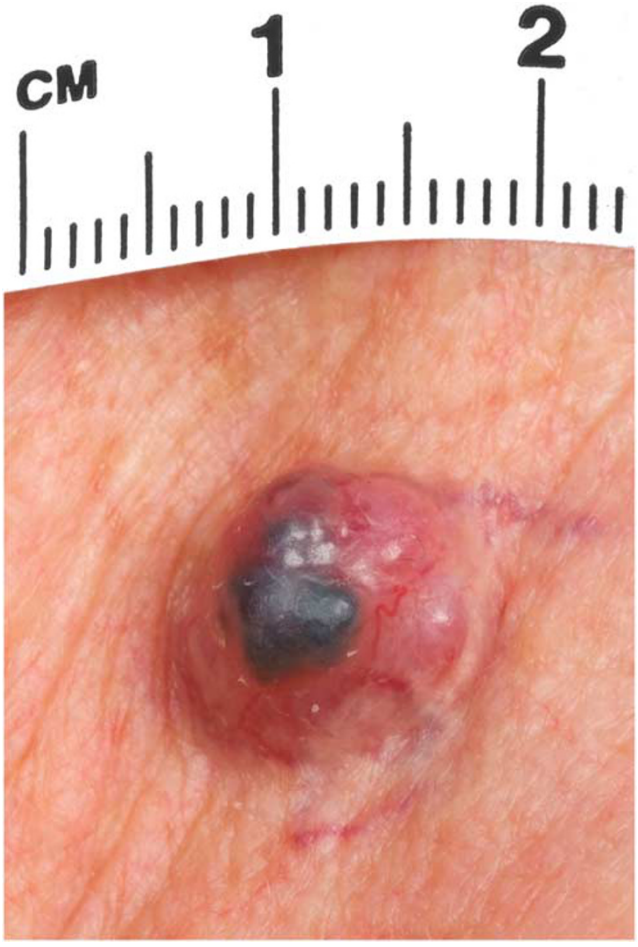

Figure 1 Low-grade spiradenocarcinoma. Clinically, the tumors present as cutaneous nodules with reddish to bluish discoloration.

Immunohistochemistry

The results of the immunohistochemical studies for *p53*, Ki-67, and *MYB* are summarized in Table 2.

P53 expression. Tissue was available for p53 staining in 18 tumors. However, benign and malignant aspects of the tumor could be compared in 13 cases only, as no benign component was represented in the tissue sections in five cases. P53 was expressed in both the benign and malignant components. Increased expression in the malignant over the benign aspect was noted in 5 of 13 tumors only. The overall intensity of p53 expression and the percentage of positive tumor cells were similar in the benign (range: 15–80%; median: 56%) and malignant (range: 10–90%; median: 67%) components; there were no statistically significant differences between the two groups (Figure 6a).

Ki-67 proliferative index. All cases were stained with antibodies to Ki-67. However, tissue sections of five cases contained no discernible benign components for comparison. In 10 of 14 cases the Ki-67 proliferative index was increased in the malignant component. The overall Ki-67 proliferative index ranged from 0 to 11% (median: 5%) in the benign and 0 to 24% (median 8%) in the malignant components. The differences were subtle

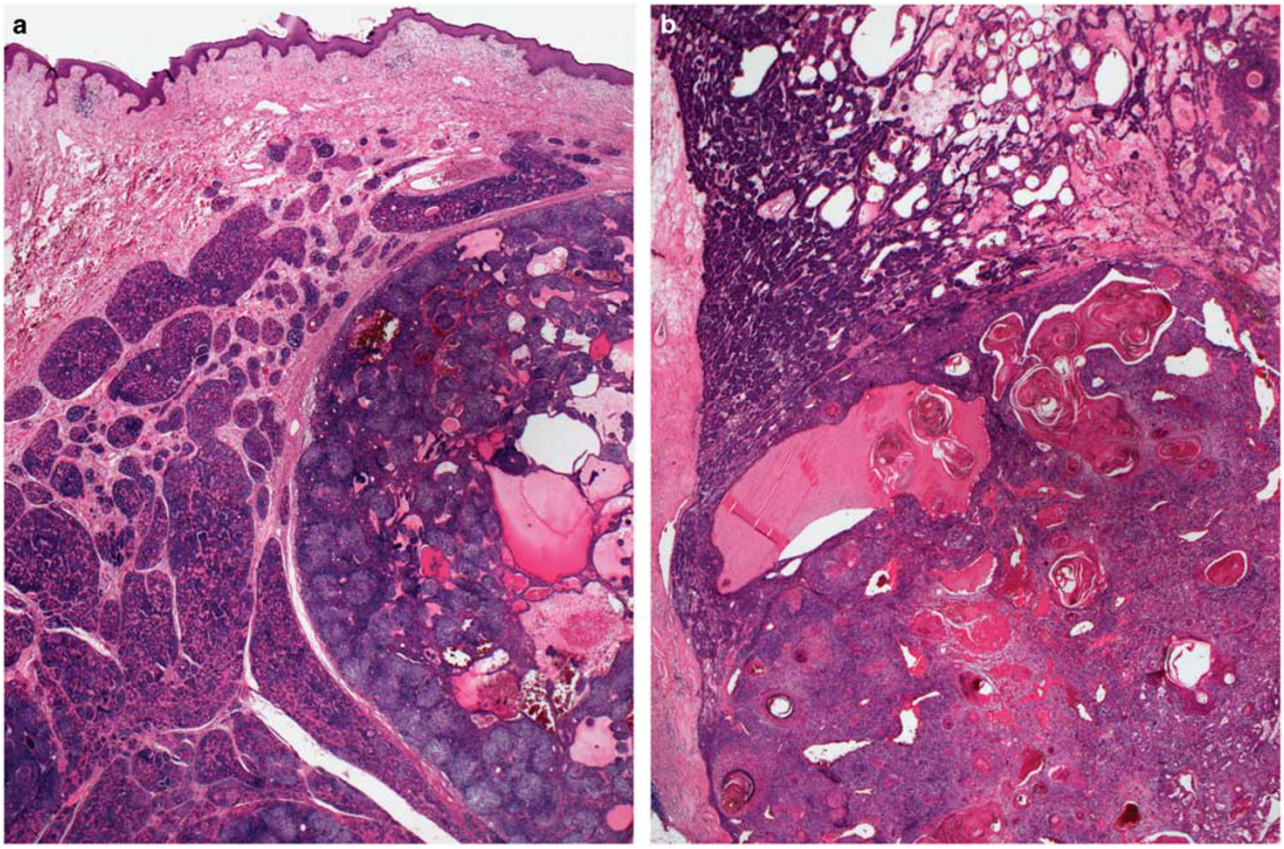

Figure 2 Low-grade spiradenocarcinoma. These dermal-based tumors are characterized by a multinodular architecture. A pre-existing benign spiradenoma is present at the left hand side. The area of malignant transformation shows an expansile growth (right hand side) (**a**). The margins are pushing rather than infiltrative (**b**).

yet statistically significant with a *P*-value of 0.0059 (Figure 6b).

MYB expression. Nuclear MYB staining was present in all dermal cylindromas (median: 34%; range: 15–50%; $n=10$), eccrine spiradenomas (median: 22%; range: 10–50%; $n=10$), and the one spiradenoma–cylindroma hybrid tumor (10%) (Figure 7a and b). Tissue for MYB staining was available for 16 low-grade malignant spiradenocarcinomas. However, an additional pre-existing benign component was present in tissue sections of only 12 cases. In eight cases the pre-existing benign component was scored as negative with no staining at all in two cases and weak staining ranging from 1 to 5% in six cases. The benign counterparts in four cases scored positive for MYB expression, ranging from 10 to 50%. The malignant components of all 16 low-grade spiradenocarcinomas scored negative (Figure 7c). Only two cases showed weak positivity in 5% of the tumor cells, whereas the remaining 14 tumors demonstrated no MYB staining. The differences in MYB expression between the benign and malignant components of the spiradenocarcinomas were statistically significant with a *P*-value of 0.0004 (Figure 6c).

Follow-up Data

Clinical follow-up information was available for 16 patients (84%). Two cases were too recent for follow-up and no follow-up could be obtained for one patient. The median follow-up period was 67 months (range: 13–132 months). The treatment was surgical with local excision, either as the primary treatment or following a diagnostic biopsy. Complete excision was achieved in 11 patients. Excision was incomplete in one patient and the status of the excision margin was unknown in four cases. Local recurrence was observed in three patients (19%) with a median time to recurrence of 4.5 years (range, 3–7 years). Histologically, all recurrences showed features of morphologically low-grade malignant spiradenocarcinoma, and they were similar to the initial presentation. In particular, no transformation to morphologically high-grade spiradenocarcinoma was noted. Of the patients with local recurrence, one had positive margins at the time of diagnosis; the margin status was unknown for the remaining two cases. No metastatic disease or disease-related mortality was observed. Four patients (21%) died from unrelated causes with intervals ranging from 13 to 120 months after diagnosis.

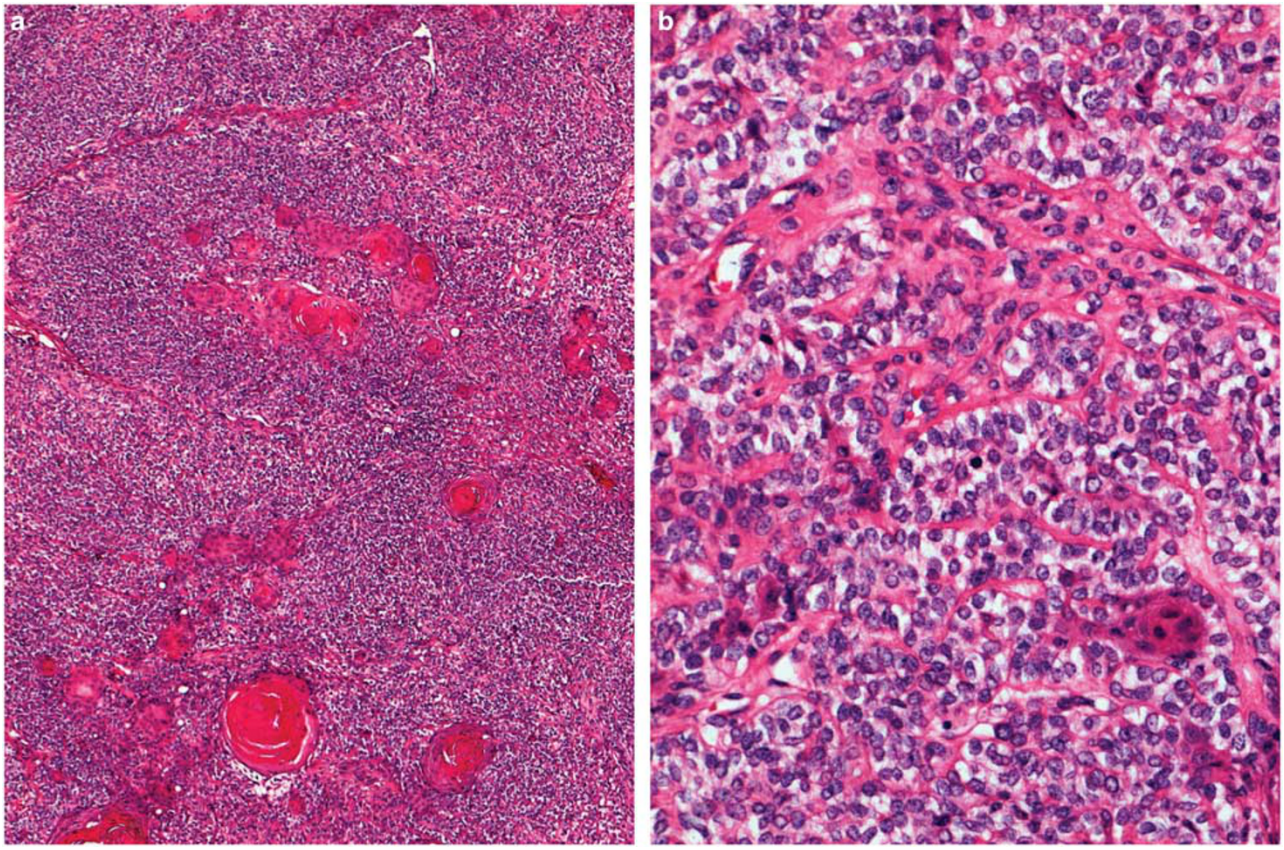

Figure 3 Low-grade spiradenocarcinoma. The malignant component is characterized by a diffuse growth pattern (**a**). The tumor cells show a monotonous growth pattern with lack of the dual cell population. Cytological atypia is mild and clear cell change may be an additional finding (**b**).

Discussion

Spiradenocarcinomas are rare malignant skin adnexal tumors. They are traditionally regarded as high-grade malignant with poor overall prognosis, characterized by potential for metastatic disease and associated mortality.[15] As yet, fewer than 100 cases are reported in the literature, mainly in case reports. With only three more comprehensive studies of 45 patients in total, little is known about the true biological potential and behavior of this disease and its prognostic parameters.[1,2,14] Histologically, the disease spectrum is separated into tumors with morphologically low- and high-grade features.[14] Kazakov *et al*[2] have further subdivided the histological patterns according to their similarities to tumors of the salivary glands into basal cell adenocarcinoma, low-grade; basal cell adenocarcinoma, high-grade; invasive adenocarcinoma, not otherwise specified; and sarcomatoid/metaplastic carcinoma. Spiradenocarcinoma showing low-grade morphology as the sole malignant component and the rare metaplastic carcinomas are currently thought to pursue a more indolent disease course.[1,2,14] However, only eighteen morphologically low-grade tumors are documented with limited clinical follow-up.[1,2,14,16–20]

On a large cohort of morphologically low-grade spiradenocarcinomas (basal cell adenocarcinoma-like pattern, low-grade) with long-term follow-up we further characterized the clinical and histological features with particular emphasis on outcome to gain further insights into the behavior of this rare disease. We also studied the value of Ki-67 and p53 immunohistochemistry as a marker for malignant transformation, and investigated the genetic relationship of these tumors to adenoid cystic carcinoma and dermal cylindroma using immunohistochemical MYB expression as a surrogate marker for the recently described t(6;9) translocation, involving the *MYB* and *NFIB* genes.[5,7,9,21]

Like other subtypes of spiradenocarcinoma, the morphologically low-grade tumors show a strong predilection for elderly adults. They present as large nodules, typically measuring multiple centimeters, with a wide anatomic distribution most commonly affecting the head and neck area followed by the extremities and the trunk.[1,2,14] While the majority occurs sporadically as solitary tumors, a small subset may be seen as malignant transformation in patients

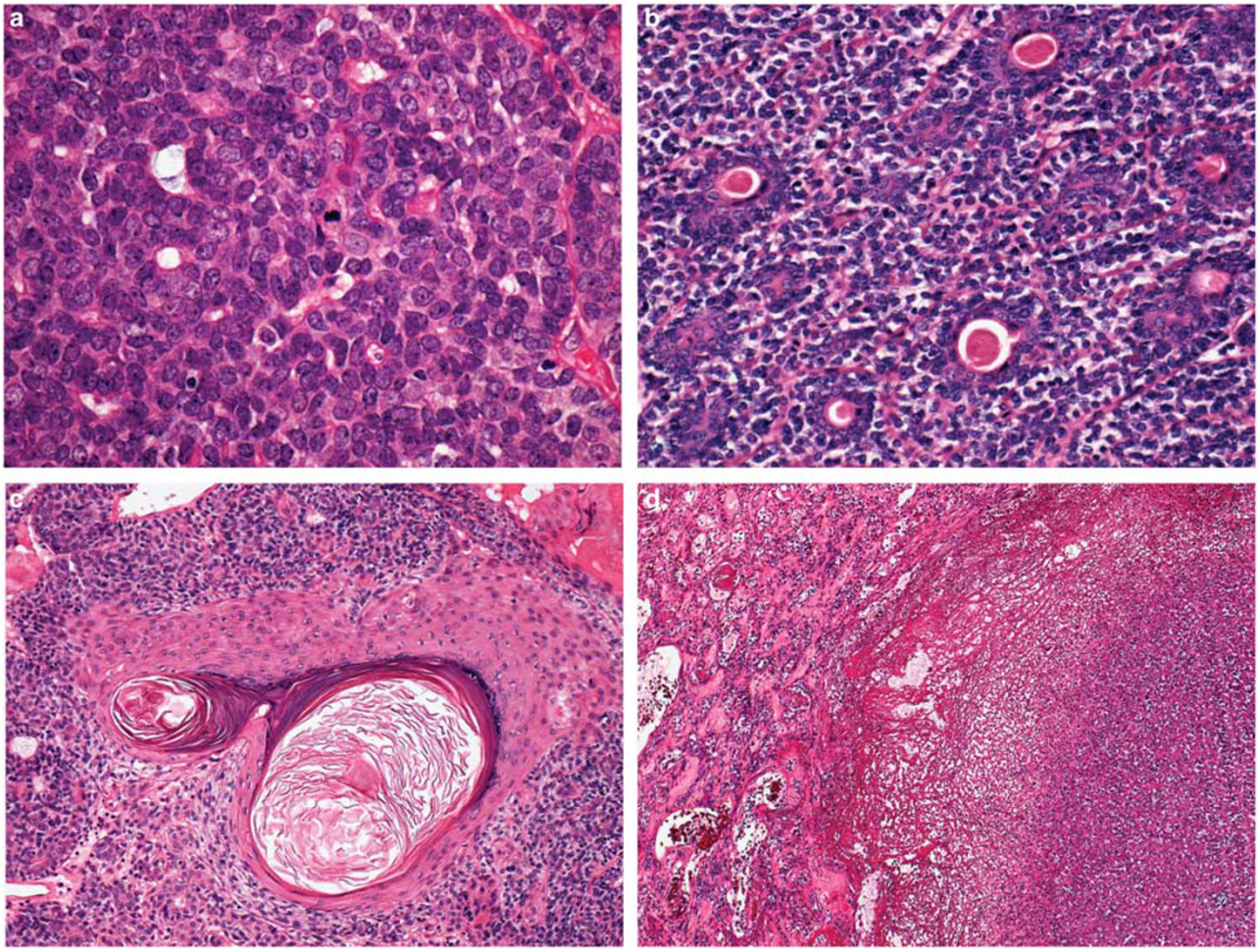

Figure 4 Low-grade spiradenocarcinoma. Cytologically, the nuclear-cytoplasmic ratio is increased, there is nuclear crowding and mitotic figures are readily identified (**a**). Additional features include duct differentiation (**b**) and keratocyst formation (**c**). Tumor necrosis may also be observed (**d**).

with the Brooke–Spiegler syndrome.[1,2,14] The histological diagnosis of low-grade spiradenocarcinoma is notoriously challenging as the morphological features are subtle and are readily overlooked. On low-power examination the tumors are multinodular with an expansile growth pattern within dermis and superficial subcutis. They are lobular and lack diffusely infiltrative margins. By definition, the recognition of a benign pre-existing spiradenoma is necessary for the diagnosis. This is often present as a minor component at the edges of the tumor only, and its identification may require careful sampling. The malignant aspect shows architectural outlines similar to the benign spiradenomatous component with which it often merges. On closer examination, the tumor cells show a more diffuse growth pattern characterized by a monotonous population of enlarged basaloid tumor cells. The tumor cells are medium sized with small-to-moderate amounts of cytoplasm and enlarged vesicular nuclei, and mitotic activity is readily identified. The presence of a dual cell population, characteristic of benign spiradenoma, is lost, a diagnostic hallmark of low-grade spiradenocarcinoma. Duct formation as evidence of its eccrine differentiation is present in varying amounts. Additional features seen in a small subset of cases are epidermal ulceration and tumor necrosis. Atypical mitoses, severe cytological atypia and marked nuclear pleomorphism are, however, absent. Owing to the notoriously subtle histological features, these tumors represent a significant diagnostic challenge and pitfall. Immunohistochemical work-up appears to be of limited use in the diagnosis of these tumors. EMA and CEA staining may prove helpful in the demonstration of duct differentiation. Occasional reports have also commented on immunohistochemical expression of p53 and an increased Ki-67 proliferative index in areas of malignant transformation.[16,19,22] However, the tumors typically lack mutations in the *TP53* gene, and our findings are in keeping with more recent and more comprehensive analyses, emphasizing that immunohistochemical staining for p53 in these tumors is heterogeneous and cannot be used reliably

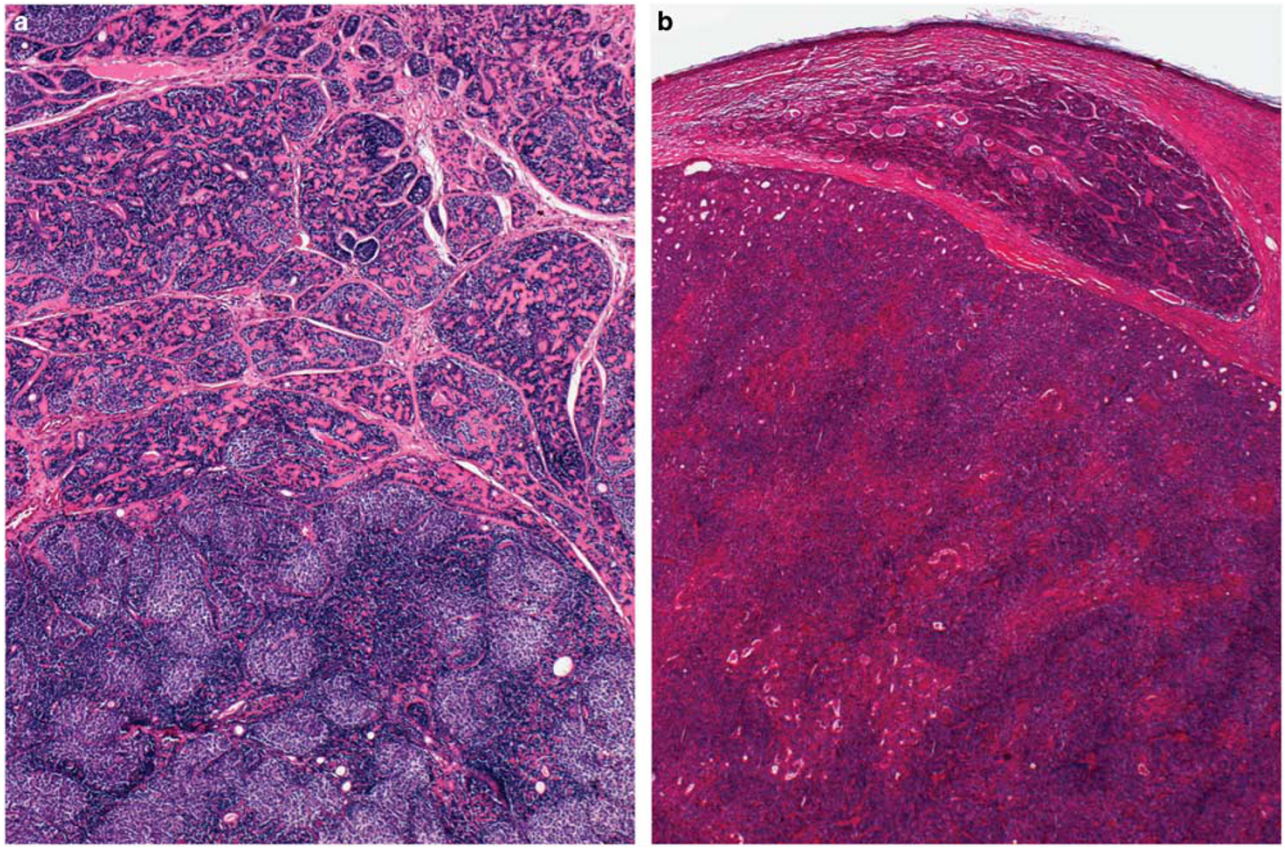

Figure 5 Low-grade spiradenocarcinoma. In the majority of cases the benign component merges with the areas of malignant transformation (**a**). In a subset of cases, there is a sharp separation of the dominant malignant component form the pre-existing benign spiradenoma, which is compressed to the side (**b**).

Table 2 Immunohistochemistry for Ki-67, p53, and MYB in low-grade spiradenocarcinoma

Case no.	*Ki-67*		*p53*				*MYB*			
			B		*M*		*B*		*M*	
	B	*M*	*%*	*Intensity*	*%*	*Intensity*	*%*	*Intensity*	*%*	*Intensity*
1	3%	6%	80%	Moderate	80%	Moderate	N/A			
2[a]	—	13%	—	—	60%	Moderate	—	—	0%	Negative
3[a]	—	11%	—	—	70%	Moderate	—	—	0%	Negative
4	4%	9%	80%	Weak	80%	Weak	20%	Weak	0%	Negative
5	1%	15%	15%	Weak	90%	Moderate	50%	Weak	0%	Negative
6	5%	11%	N/A	N/A		N/A	1%	Weak	0%	Negative
7	7%	7%	60%	Moderate	60%	Moderate	5%	Weak	0%	Negative
8[b]	4%	6%	50%	Weak	80%	Moderate	0%	Negative	0%	Negative
9	6%	6%	30%	Weak	30%	Weak	5%	Weak	5%	Weak
10	5%	8%	40%	Weak	40%	Weak	10%	Weak	0%	Negative
11[a]	—	2%	—	—	10%	Weak	—	—	0%	Negative
12[a]	—	12%	—	—	70%	Moderate	—	—	5%	Weak
13[b]	0%	0%	50%	Weak	80%	Moderate	0%	Negative	0%	Negative
14	4%	5%	70%	Moderate	70%	Moderate	5%	Weak	0%	Negative
15[b]	2%	5%	80%	Moderate	80%	Moderate	5%	Weak	0%	Negative
16[a]	—	8%	—	—	50%	Moderate	N/A			
17[a]	—	8%	—	—	80%	Moderate	—	—	0%	Negative
18	11%	24%	50%	Weak	90%	Moderate	15%	Weak	0%	Negative
19	7%	10%	50%	Weak	90%	Moderate	N/A			

Abbreviations: B, benign; M, malignant; N/A, not available.
[a]No benign parts.
[b]Limited benign parts.

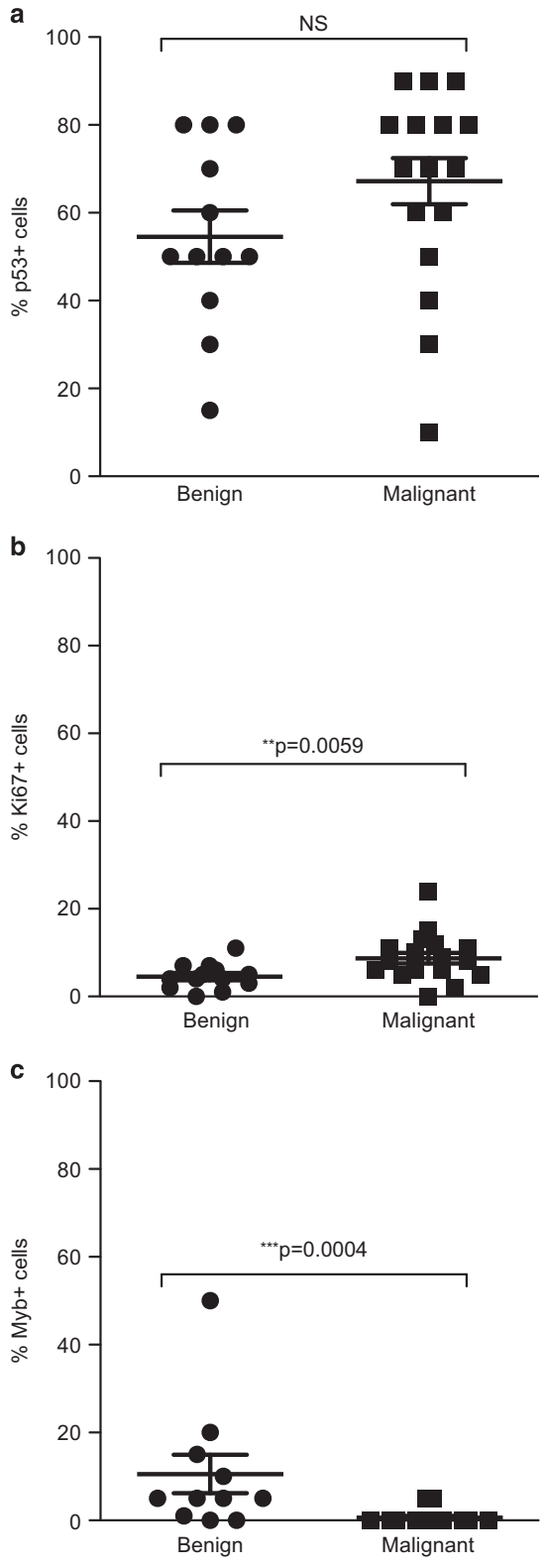

Figure 6 Immunohistochemical staining of p53 (**a**), Ki-67 (**b**), and MYB (**c**) expressed as percentages of positive tumor cells in the benign compared with the malignant components of the low-grade spiradenocarcinomas. Statistically significant increases were observed in the malignant component for Ki-67 and MYB but not p53.

to identify areas of malignant transformation.[23] Similarly, the Ki-67 proliferative index varies significantly. Although statistically significant, the differences between the benign and malignant aspects of the tumors are subtle. Similar to p53 staining, the Ki-67 proliferative index is, therefore, of little diagnostic use to highlight areas of malignant transformation.

The diagnosis and recognition of low-grade malignant tumors therefore remains a significant diagnostic challenge and rests entirely on careful histological examination and sampling with attention to subtle features to allow differentiation from benign spiradenoma. Although the morphologically high-grade tumors may be associated with an aggressive disease course characterized by distant metastases and mortality, the behavior of morphologically low-grade tumors appears to be indolent.[1,2,14] As yet, only one such case with distant metastasis and subsequent death from disease is documented.[20] Our findings further emphasize the indolent disease course, which is characterized by local recurrence. No distant metastasis and disease-associated mortality were observed with long-term follow-up, despite the presence of concerning histological features including necrosis, ulceration, and high mitotic activity. Accordingly, the treatment recommendation for low-grade spiradenocarcinoma should include complete excision and clinical follow-up. There is no need for wide margins or further surgery, including sentinel lymph node biopsy. In view of the indolent disease course and the subtle histological features, it is likely that morphologically low-grade spiradenocarcinoma is underdiagnosed and underreported in the literature.

Genetically and histologically, dermal cylindroma and eccrine spiradenoma are closely related tumors. Both may be observed in patients with the Brooke–Spiegler syndrome, and occasionally hybrid tumors with features of both spiradenoma and cylindroma are encountered.[24] Furthermore, malignant transformation has been documented in spiradenoma, cylindroma, and hybrid tumors.[1,2] Recently, a genetic link has also been established between dermal cylindroma and adenoid cystic carcinoma with both tumors sharing the t(6;9) translocation involving *MYB* and *NFIB*, resulting in MYB overexpression detectable by immunohistochemistry.[5,9] We were able to demonstrate MYB expression also in eccrine spiradenomas and a spiradenoma–cylindroma hybrid tumor, further emphasizing their close relationship with dermal cylindroma. In contrast, MYB expression was absent in the areas of malignant transformation. For the first time, these findings provide insights into potential underlying genetic abnormalities in spiradenocarcinomas; immunohistochemical staining for MYB, already used routinely as a diagnostic aid for adenoid cystic carcinoma, may prove to be an additional helpful ancillary test in the diagnosis of low-grade malignant spiradenocarcinoma.[9]

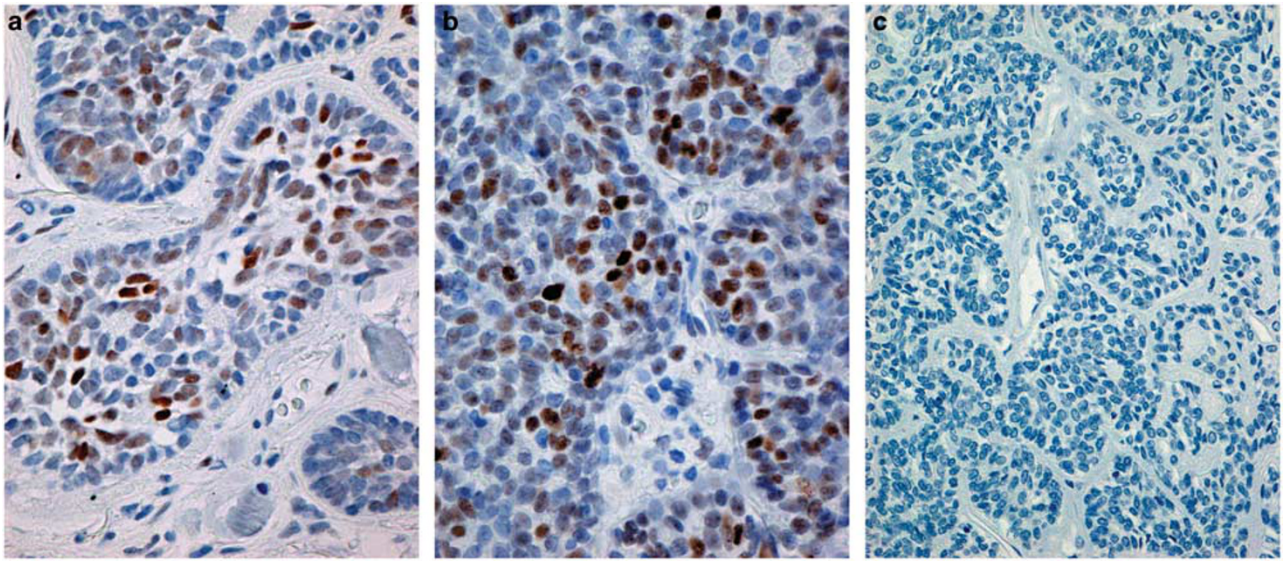

Figure 7 Nuclear expression of MYB in dermal cylindroma (**a**) and eccrine spiradenoma (**b**). No MYB expression is noted in the malignant components of low-grade spiradenocarcinoma (**c**).

The differential diagnosis of morphologically low-grade spiradenocarcinoma is wide and the correct diagnosis relies on identification and sampling of its benign counterpart. Separation from benign spiradenoma requires awareness and recognition of the subtle histological distinguishing features as outlined above. Adenoid cystic carcinoma shows many overlapping histological features and reliable separation may be difficult.[25] Primary cutaneous adenoid cystic carcinoma is characterized by a plaque-like architecture with a more diffusely infiltrative growth pattern and prominent perineural infiltration.[26] Cutaneous metastases, especially from salivary gland or breast primaries are further important considerations. Identification of an unequivocal benign preexisting spiradenomatous component is necessary to exclude this differential diagnosis.

In conclusion, this large and comprehensive study on morphologically low-grade spiradenocarcinoma further emphasizes the indolent behavior of these rare tumors. Although they may recur locally, their risk for metastatic spread or disease-related mortality appears exceptional, even with long-term follow-up. The shared MYB expression highlights the close relationship between adenoid cystic carcinoma of salivary glands and breast, dermal cylindroma and eccrine spiradenoma. Its absence in morphologically low-grade spiradenocarcinoma is a novel finding and may serve as an additional immunohistochemical marker in this difficult histological diagnosis.

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Disclosure/conflict of interest

The authors declare no conflict of interest.

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