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A squamous cell carcinoma arising from scrotal epidermal cyst. A case report and review of 94 cases from the world literature

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Epidermal cysts are a common benign skin abnormality, comprising 85–90% of all excised skin cysts. The term epidermal inclusion cyst refers specifically when the cyst resulted from the implantation of epidermal elements in the dermis. Squamous cell carcinomas (SCCs) are common skin lesions; however, a malignant transformation of an epidermal cyst is very rare with incidence of 0.011–0.045%. Few cases of malignant transformation of an epidermal cyst have been reported in the literature so far. This paper presents a case of squamous cell carcinoma arising from a scrotal epidermal cyst.

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Key words: epidermal cyst, squamous cell carcinoma, PD-1 blockade, cemiplimab

Introduction

Epidermal cysts (EC), also known as sebaceous, keratin, follicular infundibular or epidermal inclusion cysts, are extremely common lesions that can occur anywhere in the body. Histologically, they are lined with a thin layer of *squamous epithelium* and develop by buildup of keratin inside the cyst [1].The malignant transformation of an epidermal cyst is very rare clinically. Several neoplasms have been reported to develop in EC including basal cell carcinoma [2], malignant melanoma [3], Merkel cell carcinoma [4], plasmacytoma [5] and squamous cell carcinoma [6].

The development of true squamous cell carcinoma in pre-existing epidermal cysts is a rare event with incidence of 0.011–0.045% [7].

Case report

A 70-year-old male presented with a left scrotal lesion. The lesion was extra-testicular and solid. The initial clinical impression was lymphoma. A CT of chest, abdomen and pelvis was requested, which showed no evidence of lymphadenopathy or any mass lesion.

The patient underwent surgical excision of the scrotal mass. The pre-operative diagnosis and impression was that of a large sebaceous cyst. Intra-operatively, the cystic mass was accidently punctured and revealed a large amount of sebaceous fluid. The entire cystic mass was carefully dissected. The specimen was sent to Pathology.

Gross examination revealed a partially collapsed cyst measuring 3.0 x 2.0 x 1.8 cm with portion of skin attached to it.

Jak cytować:

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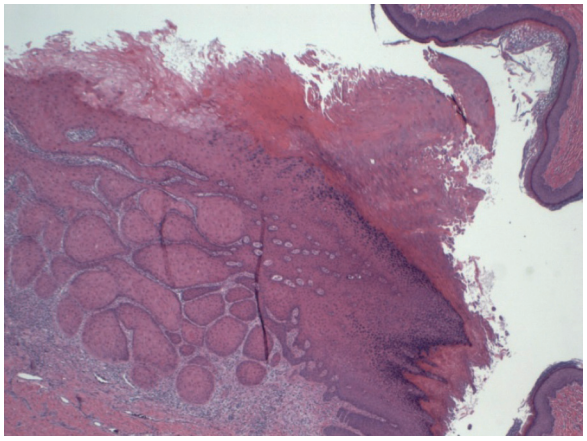

Figure 1. Low power view showing atypical squamoid nests arising from wall of scrotal epidermal cyst

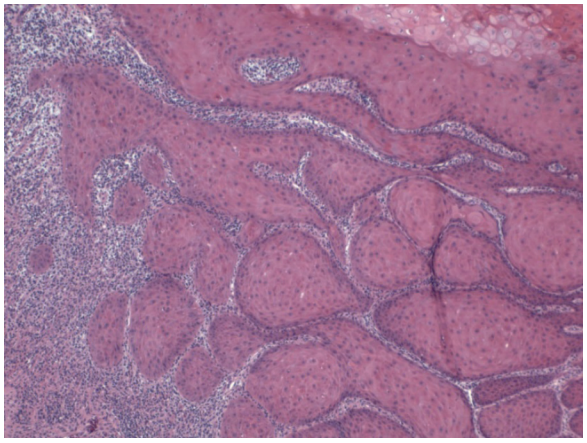

Figure 2. High power view showing the infiltrating nests of atypical squamoid cells with surrounding intense desmoplastic stromal reaction

The inner lining was smooth with the exception of one white raised area measuring 0.8 x 0.8 x 0.5 cm. The entire specimen was serially sectioned and submitted for microscopic examination. The histo-pathological examination revealed infiltrating nests of atypical squamoid cells with surrounding intense desmoplastic stromal reaction, representing an early invasive well-differentiated carcinoma arising from epidermal scrotal cyst. The resection margins were clear (Figures 1, 2).

Discussion

Epidermal cysts are common cutaneous lesions that may occur anywhere on the body. Malignant changes in the epidermal cysts are an uncommon finding.

Among the pre-malignant and malignant neoplasms that have been reported to develop in EC are: basal cell carcinoma [2, 8], malignant melanoma [3], Bowen's disease [9], Paget's disease [10], bowenoid papulosis [11], mycosis fungoides [12], Merkel cell carcinoma [4] and plasmacytoma [5]. All these lesions have a far lesser incidence than squamous cell carcinoma [6]. The development of true squamous cell carcinoma, in a pre-existing cutaneous epidermal cyst, is a rare event with incidence of 0.011–0.045% [7].

SCC also known as epidermoid carcinoma is the second most common skin cancer, after basal cell carcinoma. The rare Merkel cell carcinoma (MCC) is a frequently lethal skin cancer with a higher mortality (33%) than malignant melanoma (MM) (15%) [13]. In contrast, the survival rate for most other non-melanoma skin cancers is excellent. For instance, the 5-year relative survival for basal cell carcinoma (BCC) is 100%, whereas the 5-year relative survival for SCC is slightly less at 95% [14]. Among the above-mentioned skin malignancies, the reports show that the incidence of melanoma has been steadily rising in the recent decades [15].

The literature review revealed that in 1968 McDonald [16] analysed 637 epidermal cysts, but found malignancy in only in 7 (1.1%) cases. Of these, 6 were basal cell carcinomas and only one was a squamous cell carcinoma.

The development of SCC in EC occurs most frequently on the head and neck [17, 18], trunk [19] and thigh. Other reported sites are scrotum [20], perineal regions [7, 21], sublingual gland [22], vulva [23] and breast [24]. After reviewing all reported 94 cases, it was obvious that they are more frequent in males with incidence of 65% (Table I). The localization of the lesion was as follows: head and neck (55%), lower limbs (13%), trunk (13%), perineum (8%) and the upper limbs (6%) (Figure 3). Malignant transformation of an epidermoid cyst can also occur in the deeper parts of the body other than the skin, such as the intra-cranial region [25] and ovary [26]. It has been reported that the rate of malignant transformation of epidermal cyst into cutaneous squamous cell carcinoma ranges between 0.011% and 0.045% [27, 28]. The documented size of the affected cyst

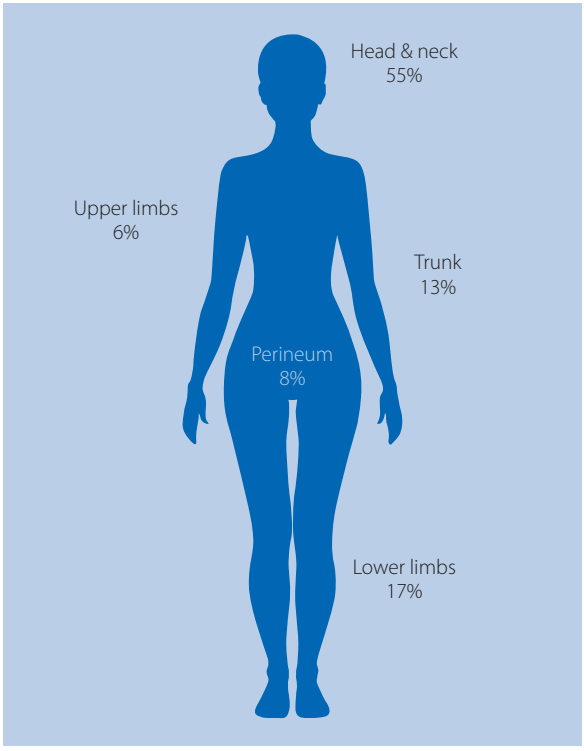

Figure 3. Distribution of 94 cases of squamous cell carcinoma developed in subcutaneous epidermoid cysts

Table I. Malignant transformation of cutaneous epidermal cyst into squamous cell carcinoma: a review of 95 cases reported in literature

Author	Year published	Gender	Age	Site	Size (mm)	Histology	Lesion duration/ months	Symptoms
Peden: 11 cases [50]	1948	F	43	scalp	–	SCC	180	↑ size
	1948	F	63	scalp	–	SCC	180	–
	1948	M	43	face	–	SCC	1	↑ size
	1948	F	64	forearm	–	SCC	1	↑ size
	1948	M	25	thigh	–	SCC	–	–
	1948	F	48	scalp	–	SCC	300	↑ size
	1948	F	63	shoulder	–	SCC	24	↑ size
	1948	F	75	scalp	–	SCC	24	↑ size
	1948	F	53	scalp	–	SCC	–	–
	1948	M	57	scalp	–	SCC	48	↑ size
	1948	M	79	ear	–	SCC	18	–
Latimer: 2 cases [51]	1949	M	40	face	40	SCC	24	ulcer
	1949	F	5	face	10	SCC	–	↑ size
McDonald [8]	1963	F	43	sternum	–		–	–
Davidson [52]	1976	M	52	ear	–	SCC	2	–
Bauer [53]	1980	M	68	preauricular	30	WD-SCC	–	inflammation
Miler [54]	1981	M	34	scalp	30	WD-SCC	240	↑ size
Yaffe [55]	1982	M	58	ear	25	SCC	132	↑ size
Arianayagam [16]	1987	F	59	thigh	25	WD-SCC	3	↑ size, pain
Sagi [81]	1988	F	60	scalp	–	WD-SCC	120	ulcer
Shah [56]	1989	F	55	buttock	90	WD-SCC	6	–
Davies [57]	1994	M	32	index finger	–	WD-SCC	120	ulcer
Malone [58]	1999	F	92	forehead	35	PD-SCC	–	↑ size
Lopez-Rios: 8 cases [23]	1999	M	68	preauricular	50	SCC	4	–
	1999	M	66	preauricular	15	WD-SCC	2	–
	1999	M	58	ear	25	SCC	132	–
	1999	M	52	ear	20	SCC	132	–
	1999	M	34	retro-auricular	80	SCC	–	–
	1999	M	32	index finger	–	SCC	120	–
	1999	F	59	thigh	50	WD-SCC	3	–
	1999	F	55	buttock	100		6	–
Wong [77]	2000	M	57	buttock	60	WD-SCC	240	↑ size
Morgan: 5 cases [34]	2001	3M	21–80 (mean 56.7)	trunk	–	WD-SCC	–	–
		2F		neck	–	WD-SCC	–	–
				face				
Debaize [78]	2002	F	38	buttock	200	SCC *in-situ*	240	↑ size
Lin [37]	2002	M	68	axilla	65	WD-SCC	2	↑ size
Cameron [59]	2003	M	67	temple	30	PD-SCC	48	↑ size, inflamed
Kume [60]	2004	M	55	sacrum	–	SCC	48	–
Nemoto [61]	2006	F	48	abdominal wall	92	PD-SCC	120	↑ size, pain
Chiu [27]	2007	M	47	thigh	130	WD-SCC	480	↑ size, bleeding
Jehle [48]	2007	M	48	gluteal area	50	WD-SCC	336	↑ size, trauma

Author	Year published	Gender	Age	Site	Size (mm)	Histology	Lesion duration/ months	Symptoms
Bhatt [22]	2008	F	64	sublingual gland	–	SCC	144	↑ size
Kuvat [31]	2009	M	48	scalp	60	SCC	156	ulcer
Ziadi [28]	2010	M	50	head	15	SCC	3	no change
Antón-Badiola [38]	2010	M	65	retro-auricular	20	MD-SCC	2	ulcer
Pusiol: 2 cases [35]	2010	M	88	face	7	SCC	–	–
	2010	M	96	ear	15	SCC	12	
Kshirsagar [39]	2011	M	72	buttock	100	WD-SCC	120	↑ size, ulcer
Shabbir [62]	2011	M	M	ear	12	SCC	–	–
Moritt: 4 cases [33]	2011	M	48	leg	–	SCC	–	↑ size
	2011	M	68	back	–	SCC	72	↑ size, inflamed
	2011	F	72	scalp	–	SCC	240	↑ size, ulcer
	2011	F	60	face	–	SCC	3	↑ size
Anastasios [63]	2012	F	69	face	9	MD-SCC	18	↑ size
Terada [42]	2012	F	76	nasal		SCC	–	cosmetic
Sumi [64]	2012	F	76	labia majora	125	WD-SCC	–	↑ size
Sinha [65]	2012	M	65	scalp		WD-SCC	72	↑ size
Pusiol: 4 cases [35]	2012	M	88	face	–	SCC	–	–
	2012	M	96	ear	15	SCC	–	–
	2012	M	67	hallux	8	SCC	–	ulcer
	2012	F	86	perineum	15	SCC	–	–
Tokunaga [30]	2013	M	65	neck	90	PD-SCC	420	↑ size, bleeding
Yeh [20]	2013	M	86	scrotum	41	WD-SCC	276	discharge
Cappello [47]	2013	M	63	nasal skin	20	WD-SCC	36	pain, discharge
Skroza [66]	2014	M	63	scalp	30	SCC	24	–
Hasegawa [67]	2014	M	75	buttock	60	SCC	–	–
Fujita [68]	2015	M	48	pre-sacral	120	SCC	1	pain
Satoh [69]	2015	M	76	pre-sacral	70	SCC	36	↑ size
Sridevi [21]	2015	M	68	submandibular	60	WD-SCC	12	↑ size
Suhani [24]	2015	F	60	breast	50		6	–
Sakamoto [17]	2015	M	41	thumb	20	SCC	–	ulcer
Veenstra: 3 cases [70]	2016	F	46	thigh	20	WD-SCC	12	–
	2016	F	89	supra-pubic	40	WD-SCC	1	pain, discharge
	2016	M	61	thigh	12	WD-SCC	6	↑ size
Sze [23]	2016	F	65	vulva	50	MD-SCC	240	↑ size
Lee [71]	2016	M	62	face	25	WD-SCC	–	↑ size
McAllister [36]	2017	M	73	ear	–	SCC	2	ulcer
Rathna [72]	2017	M	30	forehead	20	SCC *in-situ*	36	
Sirvastava [73]	2016	M	28	neck	65	SCC	7	↑ size
Suzuki [74]	2017	M	56	perineum	43	SCC	540	↑ size
Frank [18]	2018	F	64	neck	4	WD-SCC	48	↑ size
Zanguoie [29]	2018	F	77	neck	large	SCC	240	↑ size
Park [7]	2018	M	51	perineal	150	SCC	360	↑ size
Bears [75]	2019	M	44	thigh	15	WD-SCC	5	↑ size

Author	Year published	Gender	Age	Site	Size (mm)	Histology	Lesion duration/ months	Symptoms
Kim [76]	2019	M	46	nasal alar	9	SCC	–	–
Daisley [6]	2019	M	67	abdominal wall	150	WD-SCC	300	↑ size, pain, ulcer
Niimi [46]	2019	F	71	buttock	100	WD-SCC	12	↑ size, pain
Kasahara [79]	2019	M	50	scrotum	48	WD-SCC	24	firm
Lopez [80]	2019	M	83	peri-coccygeal	61	MD-SCC	10	↑ size, pain
Shah [81]	2019	M	37	scalp	70	PD-SCC	4	↑ size, pain
This case	2019	M	70	scrotum	8	WD-SCC	–	↑ size

WD – well differentiated, MD – moderately differentiated, PD – poorly differentiated

varies between 8 mm and 150 mm. Patients often present with a lesion size between 1 to 4 cm, and the lesion duration ranged from 2 months to 20 years [Table I].

The blamed predisposing factors include chronic history, trauma, recurrent infection, chronic sunlight exposure [29, 31], advanced age, skin that is sensitive to ultraviolet radiation, and immunosuppression [32]. Furthermore, chronic inflammation and irritation is classically described to be associated with malignant transformation in lesions behaving similarly to the epidermal cyst, such as *pilonidal sinus*, *hidradenitis suppurativa* and *chronic osteomyelitis* [33].

HPV-associated malignant transformation of the epidermal cyst in head and neck area, and the perineum has been reported before. Previous studies looked to the aetiological relation of HPV to the malignant transformation of the EC, however the limited number of cases prevents complete exoneration of HPV as an aetiological factor [29, 30, 34, 35, 36].

In the malignant transformation of the EC, the squamous cell carcinoma arises from the lining cells of the epidermal inclusion cyst. The malignancy may be associated with a sudden development of suspicious features in a sebaceous cyst, which has been present for a long time. These signs and symptoms may include the cyst changing into a firmer mass, pain, discharge, inflammation, ulceration, bleeding, rapid increase in size, inflammation or infection not responding to conservative treatment. Such findings may alert the clinician to excise the lump and examine it [7, 31, 37, 38].

Histologically, the lumen of the EC is filled with laminated keratin, and the specimen may reveal scattered islands of severely atypical neoplastic squamous epithelium arranged in small nests or sheets with marked nuclear irregularity, nuclear hyperchromasia, pleomorphism, absence of intracellular bridges, increased mitotic figures and an infiltrative growth pattern [39].

The immunohistochemistry may show positivity of the tumor cells for p53 protein, a tumor marker which is positive in malignancies including SCCs [40–42]. CK5/6 is a cytokeratin marker used to identify breast basal/myoepithelial cells [43] and together with p63+ identify squamous origin in poorly differentiated metastatic carcinomas [42, 44]. CAM 5.2 "commonly used antibody to cytokeratins 8 and CK7", is positive in most epithelial cells as in SCC [30, 45]. The suppressor protein p16 marker may also be present in SCCs [23]. Serum markers, such as SCC-related antigen level, helps in diagnosis and detection, and its upper normal is 1.5 ng/dl [26, 46]. Cytokeratin AE1/AE3 "pancytokeratin" marker, which detects most of the epithelial tissue is also found to be positive in a such cases [42, 45].

The treatment of choice in localized disease is radical surgical excision. Disease free margin specimens are recommended to avoid residual disease or recurrences. Fortunately, despite malignant transformation distant metastatic disease is rare [47]. SCC can metastasize to the regional lymph nodes and lungs [48].

Most of the cases are cured with surgery. In a small percentage of patients, the tumor reaches an incurable stage due to metastatic disease or locally advanced progression, and thus is no longer amenable to surgery or radiation therapy. At this stage palliative systemic chemotherapy or immunotherapy with PD-1 blockade using cemiplimab is indicated [32, 49].

Prognostic factors of local recurrence, metastasis, and disease-specific death, include tumor size larger than 2 cm, gender, preceding lesions, rapid tumor growth, degree of the differentiation and tumor location.

Conclusion

The malignant transformation of an epidermal cyst is a rare condition; this case illustrates the importance of patho-morphological examination of the excised epidermal cysts. Moreover, potential malignancy should be suspected in patients with chronic sebaceous cysts, and the cyst exhibits suspicious features. The most frequently affected region is the head and neck.

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