RESIDENT COMPETITION RESEARCH ARTICLES

Clear Cell Squamous Cell Carcinoma: Clinical and Histologic Parameters and a Review of the Literature

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ABSTRACT

Background: Clear cell squamous cell carcinoma (ccSCC) is an uncommon subtype of squamous cell carcinoma. This tumor subtype arises more commonly in elderly individuals and occurring greater upon sun-exposed areas of the body.

Objective: To determine the age range and locations of ccSCC, and occurrence in men as compared with women.

Methods: An observational study of ccSCC accessioned at a dermatopathology laboratory (Cleveland Skin Pathology, CSP) over an 18-month interval. Cases were retrieved and included based on a search of the terms “clear cell squamous cell carcinoma” in the diagnosis field of the CSP database and reviewed for accuracy and the degree of clear cell change in each lesion. Pathology requisition forms from these cases were used only to identify patients’ age, gender, and anatomic region of the ccSCC reviewed.

Results: Of the 17,838 cases of in situ and invasive SCC, there were a total of 107 ccSCC, 77 in situ and 30 invasive (0.6% of total SCC). Of patients with ccSCC, 71% had a history of skin cancer, many (57.9%) in the same anatomic region. When the degree of clear cell change was evaluated there was no statistically significant increase of percentage clear cell change in tumors with age.

Conclusions: Along with confirming past observations made with previous studies, our series shows that more men than women develop such tumors before 70 years of age, and more women than men after 70 years of age with men developing ccSCC on average 7 years earlier than women.

INTRODUCTION

SCC is the second most common type of non-melanoma skin cancer, of which several histological subtypes have been described.[1] One of these subtypes, the ccSCC, is an uncommon variant with relatively few case reports and studies found in the literature. Such lesions have been described clinically as nodules or ulcerated masses that can

resemble various benign and malignant cutaneous neoplasms including metastatic renal cell carcinoma.[1,2,3] ccSCC have been noted to occur more frequently on the head and neck, with a nearly equal incidence in men and women.[4]

The initial report of this SCC subtype by Kuo in 1980 describes 6 cases primarily found on the head and neck of older males with known histories of excessive sun exposure.[5] Kuo further classified these 6 cases of ccSCC into three major histologic types: keratinizing, non-keratinizing, and pleomorphic with no evidence of either glycogen or mucin present within these tumor cells cases.[5] Later studies have described mixed histological observations suggesting ccSCC having either outer root sheath, trichilemmal or even viral origin but none of these studies have been definitive in their findings.[6-9]

The focus in the limited number of studies examining ccSCC has been more on the immunohistochemical markers present as well as the histological patterns found with these lesions. The purpose of this study was to focus on the relationship this type of SCC has to age, gender, and anatomic region and also to evaluate the degree of clear cell change in lesions with respect to age and clinical distribution of ccSCC.

METHODS

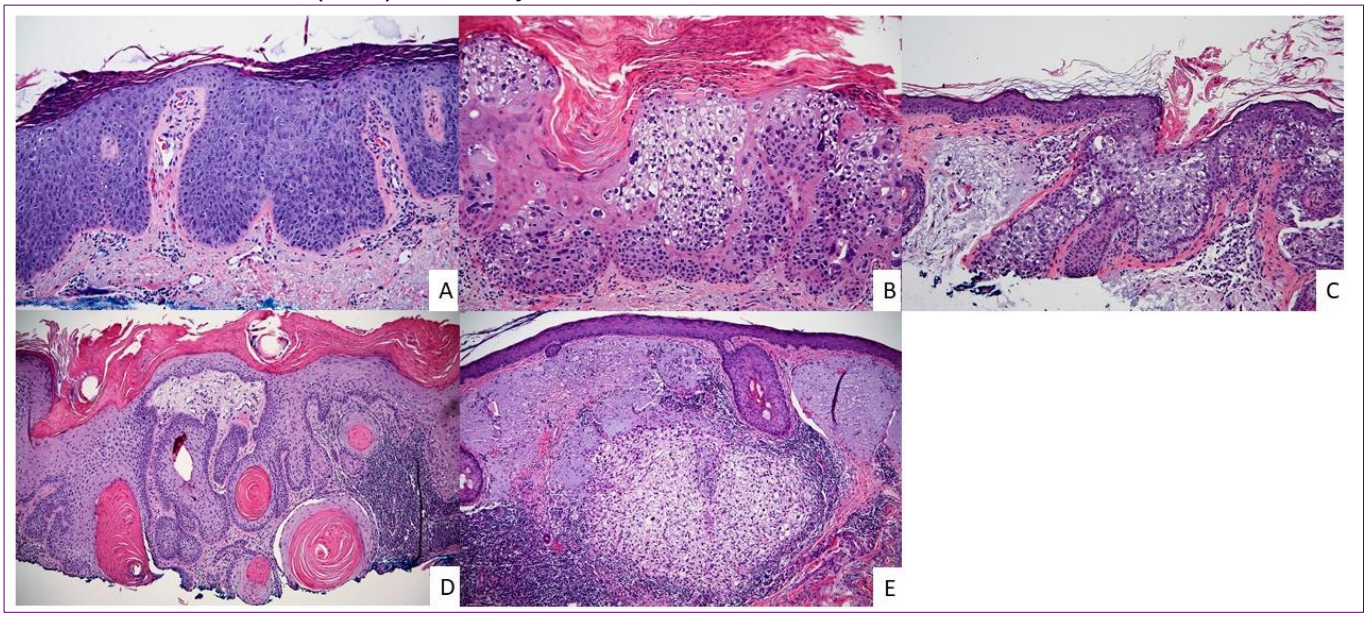
Data Source and Case Selection

All cases of *in situ* and invasive SCC (17,838 cases in total) were collected and reviewed at CSP over an 18-month interval (1/2016-6/2018). Cases were included based on search of the terms “clear cell squamous cell carcinoma” in the diagnosis field of the CSP database. All ccSCC cases included were evaluated by one dermatopathologist (CJ) for this study. Once the ccSCC diagnosis was verified, the patients’ records were checked to ensure that the same tumor was not counted twice for this study. An example of this is counting an initial ccSCC biopsy and not the later excision of a same ccSCC from an individual. Clear cell change was defined in this study as those cells that possessed clear appearing cytoplasm within the SCC on H&E (Figure 1). The ccSCC were then graded on percentage of clear cell change ranging from less than 20%, 20-40%, 40-60%, 60-80% and greater than 80%. Follicular adnexal involvement by tumor within the ccSCC lesion was also noted. Case and patient characteristics present on the pathology requisition forms were used only to identify age, gender, and anatomic region of the ccSCC lesion biopsied as well as to review the other skin cancers biopsied and read at CSP from the same ccSCC positive individual. This study was approved by the internal review board at Kansas City University of Medicine and Biosciences.

Statistical Analysis

Analysis of the ccSCC cases was completed using Microsoft Excel software. Frequency and relative frequency distribution diagrams were used to analyze this case population for the following criteria: 1) occurrence of total cutaneous ccSCC in the age ranges describe previously, 2) percentage level of clear cell change within ccSCC lesions over the designated age ranges, and 3) percentage of clear cell change within ccSCC by anatomic site. Chi-squared analysis was used to determine the significance of the proportion of age less than 70 years and above 70 years with respect to gender. Student’s two-sample t-test was used to determine significance between average age of diagnosis between gender groups.

Figure 1. Photomicrographs of both ccSCC/ccSCCIS and non-ccSCC/non-ccSCCIS lesions. A: squamous cell carcinoma in situ without clear cell change (200X) contrasted with B: clear cell squamous cell carcinoma in situ (200X); C: Adnexal extension of clear cell SCCIS; D: invasive SCC without clear cell change (100X) contrasted with E: Invasive clear cell SCC (100X). Hematoxylin-eosin stain used for A-E.



RESULTS

All cases of SCC (7,591) and SCCIS (10,247) were read between the dates of 1/2016-6/2018 at CSP. Of these cases, only 107 had clear cell change (30 invasive SCC and 77 ccSCC *in situ*) representing 0.6% of the total SCC cases read at CSP. The cases of ccSCC demonstrated a relatively even distribution between males and females (57:50) and an overall mean age of roughly 74.9 years old at time of biopsy. Of these ccSCC cases, 71% of these individuals had a history of other skin cancers in addition to their ccSCC, with 57.9% of these patients having their additional skin cancer in the same anatomic region as their ccSCC. Nearly half of all ccSCC (49.5%) showed tumoral extension into follicular adnexa.

History of additional skin cancers and their anatomic locations in ccSCC positive individuals was also tabulated from data available in CSP's database. The relative frequency analysis demonstrates that in those who have had a ccSCC and a history of other skin cancers, non-ccSCC was the most common (69.5%) followed by BCC (27.4%) (Table I). These additional skin cancers were also more likely to arise in same anatomic region as their ccSCC, with the head and neck region (56.5%) being the most frequent for this to occur.

Age differences among males and females diagnosed with ccSCC were examined in those who were less than 70 years of age and those greater than 70 years of age. From this analysis using Chi-squared testing, there was a statistically significant greater proportion of males diagnosed with ccSCC (43.9%) than females (18.0%) less than 70 years old in this sample (p=0.0042) (Table II). From this sample of ccSCC cases, the average age at diagnosis for ccSCC was 7 years earlier for males than for females, a difference that was also statistically significant (71.7 years for

males vs. 78.7 years for females, p=0.003) (Table II).

Two-way frequency analysis was used to examine the relationship trends of clear cell change within these ccSCC cases by age bracket as well as by the anatomic origin of the ccSCC lesion (Figure 2A&B). In these observational analyses, the degree of clear cell change increased as the bracketed age range increased, peaking at 60-80% clear cell change in lesions seen between ages 70-80 (n=14, 14.1%) and 80-90 (n=13, 13.1%) years old before dropping off. There was no statistical significance of % clear cell change with age. In the analysis examining the degree of clear cell change by anatomic region, the largest percentage of clear cell change was seen on the head and neck compared to all other anatomic regions seen around the 40-60% (n=15, 15.2%) and 60-80% (n=25, 25.3%) clear cell change ranges.

Figure 2. Analysis of percent level of clear cell change of these ccSCC cases. A, Frequency histogram of percent clear cell change within ccSCCs cases by age bracket. B, Frequency histogram of percent clear cell change within ccSCCs cases by anatomic location. ccSCC, clear cell squamous cell carcinoma; Ext, extremity.

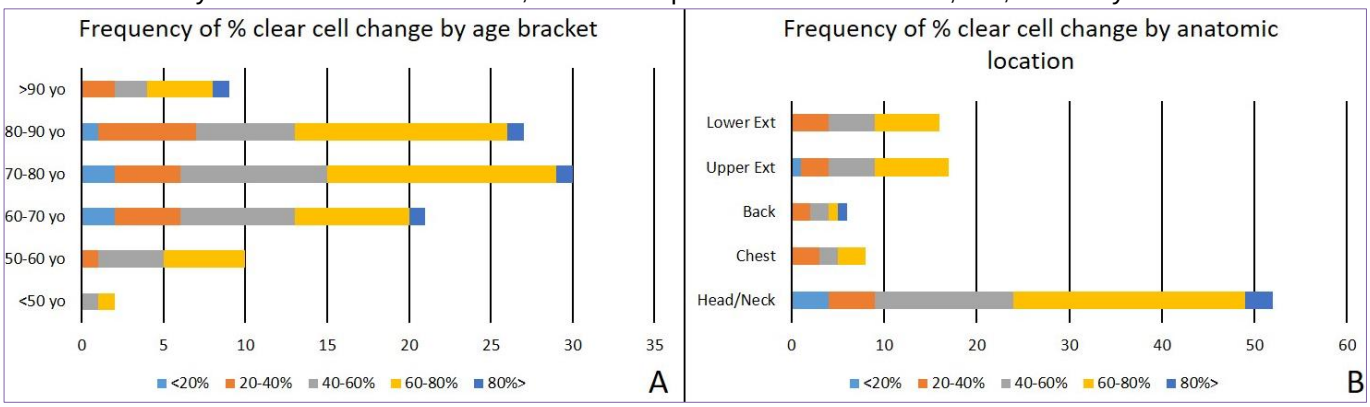


Table I. Breakdown of total SCCs reviewed at CSP and characteristics of the individuals with cases of ccSCC lesions in this study. ccSCC, clear cell squamous cell carcinoma.

SCC case breakdown of between January 2016- June 2018 reviewed at CSP	(n)	(%)
Total SCC (%)	17838	100%
SCCIS (%)	10247	57.4%
Invasive SCC (%)	7591	42.6%
Total number of clear cell SCC (%)	107	0.60%
Clear Cell SCCIS (%)	77	0.43%
Invasive Clear Cell SCC (%)	30	0.17%
Characteristics of the individuals with cases of Clear Cell SCC lesions		
Males (%)	57	53.3%
Females (%)	50	46.7%
Median Age of those with ccSCC (min,max)	76.9	36.7, 97.6
Those with history of having skin cancer other than ccSCC (%)	76	71.0%
Breakdown of total and type of these other skin cancers		
Total number skin cancers known in these individuals (%)	420	100%
With history of SCC (%)	292	69.5%

With history of BCC (%)	115	27.4%
With history of melanoma (%)	5	1.2%
With history of adnexal neoplasm (%)	3	0.7%
With history of other skin cancers (%)	5	1.2%
Those having ccSCC within same anatomic region as their history of other skin cancer	62	57.9%
Breakdown distribution frequency by these same anatomic regions		
Head/Neck (%)	35	56.5%
Chest (%)	4	6.5%
Back (%)	4	6.5%
Upper Extremities (%)	9	14.5%
Lower Extremities (%)	10	16.1%
Follicular adnexal involvement in the lesion (%)	53	49.5%

Table II. Proportion male verse female cases of ccSCC less than or great than 70 year of age and age of diagnosis between genders.

Proportion male verse female cases of ccSCC less than or great than 70 year of age						
Age Group	Males (N=57)	%	Females (N=50)	%	chi-square	*p*-value
Less than 70 yr	25	43.9	9	18.0	8.22	0.0042
Greater than 70 yr	32	56.1	41	82.0		
Age at time of ccSCC diagnosis between genders						
Sex	*n*	Mean	StdDev	StdErr	*t*	*p*-value
Males	57	71.7	13.3	1.8	3.04	0.0030
Females	50	78.7	10.1	1.4		

DISCUSSION

ccSCC is an uncommon form of cutaneous SCC related to advanced age and chronic UV radiation exposure. Our findings are consistent with prior reports that the majority of patients with ccSCC are elderly individuals, with an average age 74.9 years, and that such tumors are found more frequently on the head and neck than at other anatomic sites (Table I).[4] In addition, this study was able to determine with significance that before the age of 70, men are more likely to be diagnosed with ccSCC than women and that the average age at diagnosis for ccSCC was 7 years earlier for males than for females (Table II).

The degree of clear cell change relative to age and anatomic location demonstrates observationally as age increases; the level of clear cell change present in the ccSCC lesion is greater (Figure 2B). This is also true for those areas that are more photo-exposed, thus having prolonged UV exposure resulting in photo-damage such as that directed onto the head and neck region showed the greatest amount of clear cell change in this analysis. Together these findings are congruent with those in other ccSCC studies.[4,6,8] In our study, the most commonly

affected sites in both genders were the head and neck. The next most commonly affected sites were the upper trunk and upper extremities in men, and the lower extremities in women.

This study showed that a large percentage of individuals with ccSCC also had a history of another skin cancer (71%) with non-ccSCC and BCC being the largest other skin cancers most frequently observed in these patients (Table I). These were separate skin cancers which were also read at CSP in addition to the ccSCC cases with careful consideration to not include any duplicate pathology. Most patients, 57.9%, had additional skin cancer(s) in the same anatomic location as their ccSCC, with the head and neck being the most frequent tumor locations.

These observations underscore the role of chronic UV exposure in connection to ccSCC in attaining a threshold of actinic damage for the development of a non-ccSCC and BCC nearby. Of interest, there were two relatively younger patients with ccSCCIS in this study, 36 and 38 years old. The 36 year old had a prior history of invasive melanoma, 3 basal cell carcinomas, and multiple dysplastic nevi. No additional history was available for the 38 year old individual.

The significance of the follicular adnexal involvement remains to be fully understood. Some studies suggest ccSCC has outer root sheath or trichilemmal origin, however, observational interpretations have been mixed.[3,5] Al-Arashi et al found that some *in situ* lesions of ccSCC stain positive for PAS and immunohistochemical markers CK8.12, CAM 5.2, and CK15 suggesting outer root sheath (ORS) differentiation.[4] Misago et al confirmed that ORS markers are retained in trichilemmomas (CK17, CD34, D2-40), but did not find clear immunohistochemical evidence of trichilemmal differentiation in ccSCC.[6] Lastly, Dalton and Leboit also reviewed cases of clear cell carcinoma of the skin comparing cases to trichilemmomas with CD34, CK17, and NGFR/p75 to assess ORS differentiation. Of the cases they stained, all tumors were positive for CK17 but only 2 cases stained with CD34 or NGFR/p75, indicating that ccSCC does not show trichilemmal differentiation.[7]

Separately, Corbalan-Velez et al described two histologic patterns in the SCCs with clear-cell changes in their reported cases. First was a pattern with clear-cells around keratin pearls more commonly found with prior actinic keratosis (AK) and what they believed to be indirect signs of HPV within the infundibulum of lesions. The second pattern observed resembled adnexal differentiation associated with prior Bowens disease.[8] Cohen at al reported two cases of facial ccSCCIS, both on the cheeks of an elderly husband and wife. Each had a ccSCCIS with HPV present, however, one contained HPV 5 and the other HPV 21, respectively, suggesting that HPV DNA may be a factor in the development of ccSCC.[9] Clear cell change may arise for various reasons and its etiology remains uncertain, as a review of the literature (Table III) indicates.

Table III. Literature review and summary of prior ccSCC studies. ccSCC, clear cell squamous cell carcinoma. ccSCC, clear cell squamous cell carcinoma; N/D, not done

Study	Cases	Gender	Age	PAS	PAS with diastase	Immunoperoxidase	ORS by Immunoperoxidase	HPV	Summary/ Miscellaneous Findings
Kuo T (5)	6	6 M	52-80	-	N/D	N/D	N/D	N/D	negative Oil red O stains
Lawal AO et al (1)	1	M	62	-	N/D	AE1/AE3 +	N/D	N/D	
Al-Arashi MY, Byers HR (4)	80	N/D	N/D	+	N/D	CK 7,10,18,19; neg CK15 pos in 50%	14/80 cases stained, and were +	N/D	Clear cell change in SCCIS is part of the spectrum which displays ORS differentiation
Cohen PR et al (9)	2	1 M, 1 F	80		N/D	N/D	N/D	+	Consort SCCIS containing HPV in clear cells of facial lesions of an octogenarian couple
Corbalan-Velez R et al (8)	122	not stated	Avg. 73.4	+	N/D	CD34,EMA, CEA	N/D	analysis not possible	Suggestive of adnexal differentiation
Dalton SR, LeBoit PE (7)	40	29 M, 11 F	56-91	95% +	95% +	CD34,CK17, NGFR/p75	85% negative for ORS markers	N/D	Well-differentiated trichilemmal carcinoma is rare
Misago N, et al (6)	10	3 M, 7 F	65-90	variable	variable	CK1,CK10,CK17, CD34, D2-40		N/D	No clear immunohistochenical evidence of trichilemmal differentiation in ccSCC
Requena L et al (3)	1	M	62	not in clear cells	N/D	high/low molecular weight cytokeratins +	N/D	N/D	Electron Microscopy saw vacuoles without lipid

In this study, the percentage of specimens that showed follicular involvement with ccSCC lesions (Table I) was 49.5%, and reflects sampling of the tumors in routine sections. Whether this indicates tumor extension to be associated with relative epidermal atrophy, or with aging and exposure of follicular ostia to oxidative and UV stress is not known.

This study of ccSCC is limited in that ccSCC is a rare subtype of SCC. Acquiring larger numbers of tumor takes time to accrue, therefore an observational retrospective study was used. In addition, our findings may be regionally dependent as other geographic zones may experience varying results depending on climate, environment, and cultural practices that can affect solar

exposures habits. Also, limited history was available in those persons who had ccSCC cases, since there was only access to the information present in the CSP database. Review of the literature and this study of ccSCC do not indicate if the degree of clear cell change correlates with prognostic outcomes in comparison with other clear cell lesion subtypes, such as the odontogenic, salivary, oral squamous cell and metastatic variety; all of which are known to have a more aggressive biologic behavior.[10,11] The literature on ccSCC to date suggests that this subtype has an intermediate potential for metastasis when compared to other SCC subtypes but more studies are needed to better understand ccSCC behavior.[2]

CONCLUSION

In summary, this study validates past observations that ccSCC occur more commonly in elderly individuals in areas of high photo-exposure such as the head and neck. This study identifies that men under the age of 70 are not only at greater risk of this type of SCC but are also diagnosed on average 7 years earlier than females. In addition, our findings demonstrated that individuals who had ccSCC likely had an additional non-clear cell skin cancer present in the same anatomic region. Further research is still needed to better understand the nature and behavior of this rare cutaneous SCC subtype.

Keywords: Clear Cell, Squamous Cell Carcinoma, Dermatopathology

Abbreviations:
BCC: basal cell carcinoma
ccSCC: clear cell squamous cell carcinoma
ccSCCIS: clear cell squamous cell carcinoma *in situ*
CSP: Cleveland Skin Pathology
HPV: human papilloma virus
ORS: outer root sheath
PAS: periodic acid–Schiff
SCC: squamous cell carcinoma
SCCIS: squamous cell carcinoma *in situ*
UV: ultraviolet

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