Catastrophic cutaneous carcinomatosis in the non-organ transplant patient

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Background: The increased frequency of nonmelanoma skin cancers (NMSCs) in organ transplant recipients has been termed "catastrophic cutaneous carcinomatosis" (CCC). We have treated a cohort of immunocompetent patients with an increased number of NMSCs that meets the definition of CCC whom we have termed "catastrophic cutaneous carcinomatosis-immunocompetent" (CCC-IC).

Objective: We sought to further understand the epidemiologic characteristics of this subset of immunocompetent patients with a high burden of NMSCs.

Methods: Our pathology database was searched over a 4-year experience of a Mohs surgeon to identify patients with greater than 10 basal cell carcinomas (BCCs) and/or squamous cell carcinomas (SCCs) in a 12-month period who had no underlying systemic cause of immunosuppression or genetic predisposition to form NMSCs. Information regarding the 13 patients who met inclusion criteria was collected by questionnaire and analyzed.

Results: There was no statistically significant difference in the constitutional variables of this patient population. Patients with CCC-IC had a SCC:BCC ratio of 2.5:1, similar to what is seen in organ transplant recipients where the SCC:BCC ratio is 2:1 with SCC predominance. There was a statistically significant increase in the number of SCCs in patients with CCC-IC (8.77/patient) as compared with control patients (2.27/patient). Most strikingly, a 13.8-fold higher incidence of malignant melanoma in the CCC-IC group was found as compared with the general population.

Limitations: Limitations to this study include a small sample size and recall bias.

Conclusion: Our data suggest that patients with CCC-IC have skin cancer profiles of SCC and BCC similar to organ transplant recipients and have a markedly higher incidence of malignant melanoma than the general population. These patients require strict monitoring and combination therapeutic approaches toward management of cutaneous carcinomas. (J Am Acad Dermatol 2011;64:536-41.)

Key words: basal cell carcinoma; catastrophic cutaneous carcinomatosis; immunocompetent patients; nonmelanoma skin cancers; squamous cell carcinoma.

Catastrophic cutaneous carcinomatosis (CCC) is described as development of at least 10 distinct nonmelanoma skin cancers (NMSCs) in organ transplant recipients (OTRs) within 1 calendar year.[1] The occurrence of this high burden of NMSCs is rare and carries high morbidity. OTRs are at increased risk of having both systemic and cutaneous cancers, with an overall increased risk 3- to 4-fold greater than that of the general

Abbreviations used:

BCC:	basal cell carcinoma
CCC:	catastrophic cutaneous carcinomatosis
CCC-IC:	catastrophic cutaneous carcinomatosis with immunocompetence
NMSC:	nonmelanoma skin cancer
OTR:	organ transplant recipient
SCC:	squamous cell carcinoma
UV:	ultraviolet
UVR:	ultraviolet radiation

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population.[2] In our cutaneous oncology practice in a tertiary care academic medical center, we have observed a pattern of cutaneous carcinomatosis meeting the definition of CCC occurring in immunocompetent (CCC-IC) patients without a history of organ transplant or immunosuppression. These patients appeared to develop many NMSCs when compared with patients who develop sporadic skin cancer. To our knowledge, the epidemiologic characteristics of this group of patients have not been previously described in the literature. These patients also represent treatment challenges as we weigh the associated morbidity of multiple cutaneous surgeries against alternate treatment modalities with lesser cure rates (ie, imiquimod, 5-fluorouracil, electrodessication and curettage). We therefore conducted a case–control study, comparing a series of patients with CCC-IC to patients with sporadic cutaneous carcinomas.

CAPSULE SUMMARY

- We have treated a cohort of immunocompetent patients with an increased number of nonmelanoma skin cancers that meets the definition of catastrophic cutaneous carcinomatosis.
- Our data suggest that patients with catastrophic cutaneous carcinomatosis and immunocompetence have skin cancer profiles of squamous cell carcinoma and basal cell carcinoma similar to organ transplant recipients and have a higher incidence of malignant melanoma than the general population.
- These patients require strict monitoring and combination therapeutic approaches toward the management of cutaneous carcinomas.

METHODS

This study was performed with approval of the Institutional Review Board at Mount Sinai Medical Center, New York, NY. A case-control study was designed to identify patients with cutaneous carcinomas. First, our institutional pathology database was searched between January 1, 2002, and December 31, 2006, for all patients with a pathological diagnosis of basal cell carcinoma (BCC) and/or squamous cell carcinoma (SCC) who had a total of more than 10 pathology specimens in the system (inclusive of all surgical specimens, not limited to skin). We identified 5399 patients who met the criteria of having a diagnosed BCC and/or SCC and 10 or more pathology specimens in their record. We then performed a patient-by-patient online medical record review of all 5399 patients searching for patients with 10 or more pathologically confirmed BCCs and/or SCCs in a 12-month period. We identified 71 individuals with 10 or more BCCs and/or SCCs in a 12-month period from this pool of patients. Of these 71 patients, 51 were not patients of our dermatology faculty practice and were not solicited for further information, thus leaving 20 patients. Exclusion criteria were defined as patients with prior systemic malignancy such as lymphoma; history of receiving chemotherapy, radiation, or psoralen plus ultraviolet (UV) A; history of immunosuppressive disease such as HIV/AIDS or receiving immunosuppressive medications; history of genetic cutaneous carcinoma syndromes including nevoid BCC syndrome or xeroderma pigmentosum; or history of organ transplant. Of the remaining 20 patients, 4 refused to participate and 4 were prior transplant recipients. Thus, a total of 12 patients were identified in the database plus one additional clinical case that met all inclusion criteria and these were included in the study. An age- and sex-matched randomly selected group of control patients who were treated for NMSC was identified from patient referrals within the same faculty practice. These patients were not identified in the database as having 10 or more pathologically confirmed BCCs and/or SCCs in a 12-month period.

A retrospective analysis of the case and control patients' charts was conducted. In addition, a questionnaire was sent to all case and control patients to collect demographic and epidemiologic data variables under investigation. Characteristics included Fitzpatrick skin type, prior UV exposure, hair color, eye color, number and sites of skin cancers, exposure to known carcinogens, history of radiation exposure, family history of skin cancer, sunscreen use, underlying health problems, and medications. Follow-up telephone calls were made to individuals for any missing data or clarification of responses. All statistical analyses were conducted using software (SAS v9.1, SAS Institute Inc, Cary, NC). Means of continuous variables for case and control groups were compared using the two-sample t test. Given the small sample size, for categorical variables with two (unordered) categories, case and control groups were compared using Fisher exact test. For categorical variables with more than two ordered categories (eg, frequency of outdoor activity), case and control groups were compared using the Cochran-Armitage trend test to assess trends in binomial proportions across a single covariate. The investigational data for both groups (CCC-IC and control) are summarized in Table I.

Table I. Distribution of predisposing variables and skin cancer diagnoses

Variables	Case, N = 13	Control, N = 17	*P* value
Age, y (mean)	77.38 (12.28)	74.35 (12.28)	.5162
Sex, N (%)			Fisher exact *P*
Female	5 (38.46)	6 (35.29)	1.0000
Male	8 (61.54)	11 (64.71)	
Skin type (%)			Cochran-Armitage trend test
I	8 (61.54)	10 (58.82)	Z = 0.4716
II	5 (38.46)	6 (35.29)	.7567
III	0 (0.00)	1 (5.88)	
Eye color (%)			
Blue	4 (30.77)	11 (64.71)	.0552
Brown	8 (61.54)	3 (17.65)	
Green	1 (7.69)	3 (17.65)	
Hair color (%)			
Black	0 (0.00)	3 (17.65)	.0873
Blond	3 (23.08)	6 (35.29)	
Brown	10 (76.92)	6 (35.29)	
Red	0 (0.00)	2 (11.76)	
Family history (%)			
No	10 (76.92)	12 (80.00)	1.0000*
Yes	3 (23.08)	3 (20.00)	
Residence before 18 y (%)			
North	11 (84.62)	12 (92.31)	1.0000*
South	2 (15.38)	1 (7.69)	
Occupation (%)			
Indoor	11 (84.62)	15 (88.24)	1.0000
Outdoor	2 (15.38)	2 (11.76)	
Severe sunburns (blistering) (%)			Cochran-Armitage trend test
None	6 (46.15)	0 (0.00)	Z = 1.0818
1-4	3 (23.08)	12 (70.59)	.3488
5-8	2 (16.38)	3 (17.65)	
9-12	1 (7.69)	0 (0.00)	
13-16	1 (7.69)	2 (11.76)	
Severe sunburns (blistering) (%)			
No	6 (46.15)	0 (0.00)	.0029
Yes	7 (53.85)	17 (100.00)	
Sun protection (%)			
No	13 (100.00)	5 (29.41)	.0000
Yes	0 (0.00)	12 (70.59)	
Outdoor activity (%)			Cochran-Armitage trend test
None	3 (23.08)	1 (5.88)	Z = 0.0437
Infrequent	1 (7.69)	7 (41.18)	1.000
Often	3 (23.08)	11 (5.88)	
Frequent	6 (46.15)	8 (47.06)	
History of BCC (mean)	3.54 (3.41)	1.73 (1.98)	.0931
History of SCC (mean)	8.77 (4.42)	2.27 (3.26)	.0001
Skin cancer total (mean)	12.69 (2.87)	4.29 (4.47)	<.0001
Age at first skin cancer, y (mean)	59.37 (14.36)	67.06 (14.79)	.1650
History of Melanoma (%)			
No	9 (69.23)	17 (100.00)	.0261
Yes	4 (30.77)	0 (0.00)	

BCC, Basal cell carcinoma; *SCC*, squamous cell carcinoma.
*Calculation based on participant with nonmissing data.

RESULTS

Demographics

The mean ages of the control and case patients were similar. The mean for the control group was 74.35 years (SD = 12.28) whereas the mean for the CCC-IC group was 77.38 years (SD = 12.28). Sex was well matched between the control group (35.29% female, 64.71% male) and the case group (38.46% female, 61.54% male).

Skin cancers

There was no statistically significant difference in the mean age of the first skin cancer between the control and the case groups. With regard to the type of skin cancer, there was no significant difference in the mean number of BCCs between the control and case groups (3.54 and 1.73, respectively). However, there was a significant difference in the mean number of SCCs between the two groups ($P < .01$). The mean number of SCCs per patient in the control group was 2.27 (SD = 3.26) whereas in the CCC-IC group the mean number per patient was 8.77 (SD = 4.42). Further, a statistically significant difference in the percent of patients with melanoma existed between the two groups ($P < .05$). Although no control patients had a history of melanoma, among the patients with CCC-IC, 30.77% had a history of at least one melanoma. Correspondingly, there was a statistically significant difference in the mean number of total skin cancers between the two groups ($P < .01$). Although the mean number of total skin cancers per patient in the control group was 4.29 (SD = 4.47), the mean number of total skin cancers per patient in the CCC-IC group was 12.69 (SD = 2.87).

Predisposing variables

There was no significant difference in the distribution of eye color or hair color between the two groups of patients. Likewise, no significant difference in geographic distribution existed between the control and CCC-IC groups. No difference existed between the groups in terms of family history of skin cancer as 20% of control patients and 23.08% of patients with CCC-IC reported a positive history. With regard to occupation, 11.8% of control patients and 15.38% of patients with CCC-IC reported having an outdoor occupation. Nevertheless, there was no significant difference between the groups. There was also no significant difference in the distribution of outdoor activity between these two groups.

Of note, there was no significant difference among Fitzpatrick skin types between the two groups. Among the control patients, 58.8% had type I, 35.3% had type II, and 5.9% had type III skin. Among the CCC cases, 61.54% had type I, 38.46% had type II, and none had type III. However, there was a significant difference in the percent of patients reporting having used any regular sun protection in the past ($P < .01$). Whereas 70.6% of the control patients reported using regular sun protection, none of the CCC-IC cases reported using regular sun protection. Nevertheless, control patients reported significantly more severe sunburns than the CCC-IC cases ($P < .05$). All of the control patients (100%) reported blistering skin burns, whereas only 53.85% of the patients with CCC-IC reported severe sunburns.

DISCUSSION

We examined the association of predisposing variables in patients with CCC-IC and performed a case-control study. The interaction of these predisposing variables and the accumulation of skin cancers revealed some clinically significant differences.

The patients with CCC-IC displayed a SCC:BCC ratio of 2.5:1, similar to what is seen in OTRs where this ratio is 2:1 also with SCC predominance.[3-6] For both of these groups there seems to be a reversal of the ratio as compared with sporadic skin cancer in the general population (SCC:BCC ratio of 1:4).[5,7,8] The increased number of BCCs (3.54/patient) seen in patients with CCC-IC was not statistically significant; however, the increased number of SCCs (8.77/patient) was statistically significant. This results in an occurrence rate of BCC 2-fold higher and SCC 4-fold higher in case patients as compared with control patients. In our study group of patients with CCC-IC, no local recurrence or regional/distant metastasis has been observed. In contrast, SCCs in OTRs have been reported to recur locally in 13.4% of patients, metastasize in 5% to 8% of patients after excision,[9,10] and carry a mortality of 8%.[11-13] There was no mortality experienced in patients with CCC-IC and the absence of mortality and metastatic disease in these patients may be explained by adequate local and systemic immunosurveillance of tumors.

Our data suggest that chronic rather than episodic severe sun exposure in patients with CCC-IC results in a high burden of NMSC. Lack of sun protection coupled with chronic exposure seems to be a key risk factor in the CCC-IC group. It is generally accepted that intense UV radiation (UVR) exposure in childhood and adolescence is responsible for the development of NMSC, particularly BCC whereas chronic UVR exposure in younger years is responsible for the development of SCC.[14-17] Chronic UVR exposure not only acts as a carcinogen by inducing mutations such as p53, but also induces systemic immune suppression.[18] This localized cutaneous

and systemic immunosuppression may rapidly accelerate the development, growth, and aggressiveness of skin cancers and likely explains the induction of high numbers of skin cancers in patients with CCC-IC as in CCC-OTR.[19]

Constitutional factors, such as light eye color, light hair color, and fair skin types, have been shown to impart a greater risk of developing NMSC.[14,20-22] Brown eye color and brown hair color was more common in the patients with CCC-IC but this did not reach statistical significance in this small sample size. Lighter eye color (blue or green) was more prevalent among control patients with sporadic skin cancer in keeping with the conventional knowledge that individuals with lighter eye colors are at higher risk of developing NMSC. The patients and control subjects have predominantly fair skin types (I or II).

An important finding in this study was the statistically significant detection of increased melanoma in the CCC-IC group as compared with the control group ($P < .05$). Among the patients with CCC-IC, 30% had at least one melanoma, with a total of 6 melanomas occurring in 4 patients (3 melanomas in a single patient). None of the control patients reported history of melanoma or had a documented melanoma in the database.

In the CCC-IC group of patients, 4 participants with melanoma were observed, whereas only 0.289 cases would have been expected based on the Surveillance, Epidemiology, and End Results (SEER) incidence rates (age, sex, race adjusted), resulting in a standardized incidence ratio in the CCC-IC group of 13.8 (95% confidence interval 3.87688-35.4149). This translates into a 14-fold higher *incidence* of malignant melanoma in the CCC-IC group over the general population. In these 4 patients, there were 4 melanoma in situ cases and two stage II melanoma cases. Both stage II melanomas occurred before the year CCC-IC was diagnosed. In two patients, melanoma in situ occurred after the year in which CCC-IC was diagnosed. All melanomas were surgically treated without any history of tumor recurrence or metastasis. It is of note that in patients with CCC-OTR the risk of malignant melanoma is 3.6-fold higher than compared with the general population,[23,24] but still much lower than the 13.8-fold higher incidence seen in the CCC-IC group.

In summary, CCC-IC occurs in a distinct group of patients who develop 10 or more NMSCs in a 12 month period without a history of immunosuppression. The majority of skin cancers develop on the head and neck, signifying a role of UVR exposure. The usual ratio of SCC:BCC of 1:4 is reversed to 2.5:1 in favor of SCC in patients with CCC-IC. This group developed melanomas at a staggering rate 13.8-fold higher than the general population. Identifying patients with CCC-IC would help to increase surveillance for melanomas and other NMSCs. Fortunately neither melanomas nor NMSCs were life threatening in this group and patients were treated with excisional surgery or Mohs micrographic surgery, respectively.

Study limitations

Our study is limited by the inherit designs of a case-control study. In addition, this study is limited by the small sample size of patients who met the strict inclusion criteria. Studies with larger patient populations need to be performed. Responses to the questionnaire are limited by recall bias of the selected constitutional and exposure variables.

Conclusion

We have described a population of patients with CCC-IC in our tertiary care setting, which is an underrecognized group that may expand in the future given the increase in the overall incidence of NMSCs. The pathogenesis is likely multifactorial, including damage by direct UVR exposure, genotoxic environmental exposures, cutaneous or systemic immune changes that occur with advanced age, and genetic variability related to tumorigenesis. Although carcinogenic strains of human papillomavirus may play a role in OTRs, their role in our group of immunocompetent patients is unknown. The morbidity in the CCC-IC population is considerable and treatment is a serious challenge. We have experienced that the psychological burden and morbidity associated with CCC-IC is underestimated. These patients often cope with disease stress by denial, leading to delayed treatment and a higher risk of advanced disease. A 13.8-fold higher risk of developing melanoma calls for aggressive management and surveillance strategies. More robust studies on treatment options, however, are necessary. Further studies to define the genetics of this group and studies related to recommendations for management and early detection are forthcoming.

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