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RESEARCH ARTICLE

Epidemiological and histological characteristics of cutaneous squamous cell carcinoma and its precursor lesions – A single-center study

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Objective: Cutaneous squamous cell carcinoma (cSCC) is a skin malignancy that is one of the non-melanocytic skin cancers (NMSCs). The objective of our study was to highlight the epidemiological and histological characteristics of cSCC diagnosed in a clinical county hospital. **Methods:** A retrospective cross-sectional study was performed of histopathologically diagnosed cases of cSCC from the clinical Pathology Department of the Mures Clinical County Hospital, Târgu Mureș, Romania. We included 96 cases that were diagnosed between January 1, 2017, and December 31, 2020. **Results**: Of the 96 cases included in the study, 82 were identified as cSCC, 5 as Bowen Disease, and 9 as keratoacanthoma. The majority of the cases were diagnosed in 2018 (n = 30; 31.25%) and 2019 (n=36; 37.50%). The median age of the patients was 63.0 years. Slightly over half of the patients were male (n=50; 52.08) and 49 patients (51.04%) grew up in urban areas. Forty-six cases (56.10%) were well differentiated; 25 (30.49%) moderately differentiated, and 11 (13.41%) poorly differentiated. Almost all of the lesions (93; 96.88%) were removed within the safety excision margins. **Conclusion**: Most of the patients were diagnosed with cSCC in 2018 and 2019 and were over 70 years old. The majority were males who grew up in urban areas. Even though most of the lesions were well differentiated and completely excised surgically, the differential diagnoses between cSCC and other skin malignancies were made based on the morphological aspects of the lesions, followed by an immunohistochemical profile when necessary.

Keywords: cutaneous squamous cell carcinoma, histopathology, non-melanocytic skin cancers, skin

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Introduction

Cutaneous squamous cell carcinoma (cSCC) is a skin malignancy that belongs to the category of non-melanocytic skin cancers (NMSCs). This category also includes basal cell carcinoma and metatypical or basosquamous carcinoma [1, 2].

NMSCs represent 6.2% of the cancers diagnosed globally in 2020. Even though melanoma has a poor prognosis and is increasing in incidence, cSCC is one of the most common skin cancers, after basal cell carcinoma. Its prognosis varies depending on the stage of the lesion, the grade of differentiation, and the receipt of adequate and personalized treatment [3, 4].

cSCC develops from the epidermis as a proliferation of keratinocytes with different types of differentiation and cytological atypia. Risk factors for developing cSCC include exposure to UVA/UVB radiation, prolonged exposure to sunlight, and age. HPV virus infection and immunosuppression in patients with cancer or HIV infection can also be involved in the development of cSCC [5, 6].

The main characteristic of cSCC, in contrast to basal cell carcinoma, is that it can metastasize quickly in the absence of appropriate treatment. The precursor lesions represented by actinic keratosis, keratoacanthoma, and Bowen Disease (BD, squamous cell carcinoma in situ) can represent the earliest stages of the development of cSCC [1, 2].

Histologically, cSCC can be categorized into three main categories: well differentiated, moderately differentiated and poorly differentiated. Also, other factors such as excision margins, perineural invasion, inflammatory infiltrates, tumoral budding, the Clark level, and the type of cSCC can categorize a tumor as low or high risk [1, 7].

The COVID-19 pandemic caused by the SARS-COV-2 virus decreased access to oncologic and surgical services. This reduced opportunities for the histopathological diagnosis of cSCC, resulting in worsened patient outcomes and quality of life [8, 9].

The objective of our study was to highlight the epidemiological and histological characteristics of cSCC diagnosed in a clinical county hospital.

Materials and Methods

We performed a retrospective, cross-sectional study to examine the histopathological diagnosis of cSCC in the Pathology Clinical Department of the Mures Clinical County Hospital, Târgu Mureș, Romania. We included 96 cases diagnosed in our department between January 1, 2017, and December 31, 2021. The inclusion criterion for the cases was a histopathological diagnosis of cSCC, keratoacanthoma, or Bowen Disease made during the study period. The exclusion criteria were a histopathological diagnosis other than cSCC, actinic keratosis, keratoacanthoma, or Bowen Disease. The year of diagnosis, patient age, patient gender, patient environment of origin, the ward where the

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excision was performed, the histopathological type, the precursor lesions, the grade of differentiation, and whether the excision was within the safety margins were the parameters that were analysed. The data were collected from the histopathological reports. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Mures Clinical County Hospital (protocol code 2109/07.04.2023).

Results

The study included 96 cases: 82 of cSCC, 5 of Bowen Disease and 9 of keratoacanthoma.

Statistical data

Table I. Epidemiological and clinical data of the patients included in the study

Parameter	No. of cases	
	n	%
Year of diagnostic		
2017	13	13.54%
2018	30	31.25%
2019	36	37.50%
2020	17	17.71%
Age of the patients		
Under 40 years-old	1	1.04%
40-49 years-old	3	3.13%
50-59 years-old	15	15.63%
60-69 years-old	15	15.63%
70-79 years-old	36	37.50%
Over 80 years-old	26	27.08%
Gender of the patients		
Male	50	52.08%
Female	46	47.92%
Environment of the patients		
Rural	47	48.96%
Urban	49	51.04%
Ward where the surgical excision was performed		
Plastic and reconstructive surgery	41	42.71%
General surgery	43	44.79%
Dermatology	2	2.08%
Ophtalmology	10	10.42%

Table II. Histological data of the patients included in the study

Parameter	No. of cases	
	n	%
Histopathological type of the lesion		
cSCC	82	85.41%
Keratoacanthoma	9	9.37%
Bowen Disease	5	5.20%
Grade of differentiation of the cSCC		
Poorly differentiated	11	13.41%
Moderately differentiated	25	30.49%
Well differentiated	46	56.10%
Surgical excision within the safety limits		
Incomplete	3	3.13%
Complete	93	96.88%

Morphological data

Figure 1 presents the grading of the cSCC based on the differentiation: well differentiated (A), moderately differentiated (B) and poorly differentiated (C).

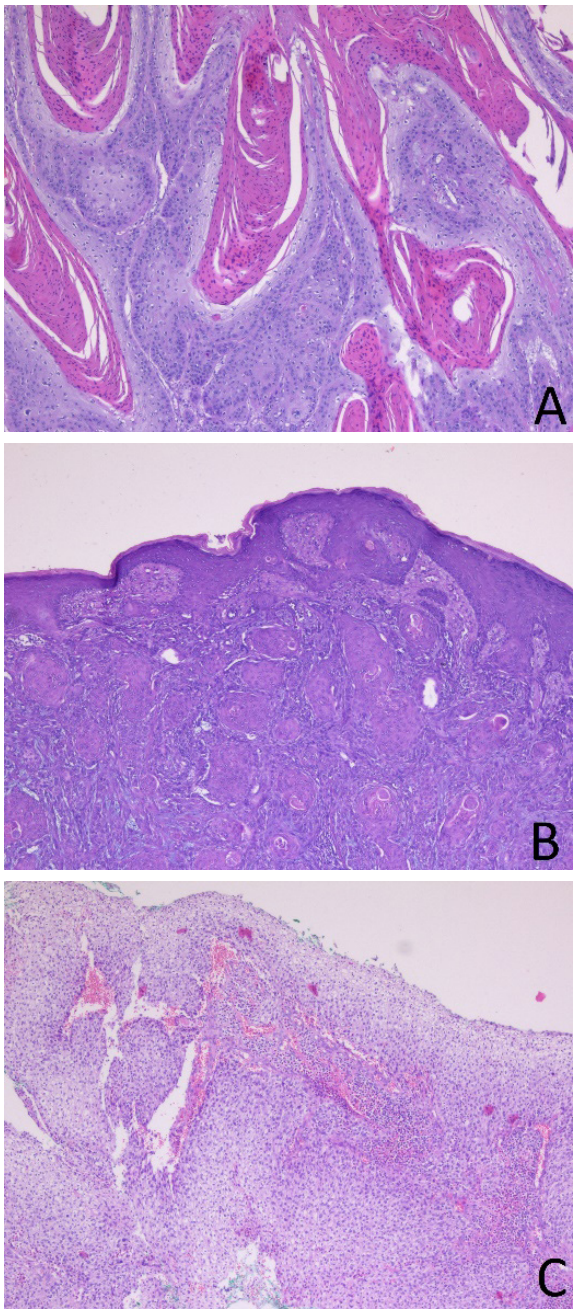

Fig. 1. Histopathological variants of the cutaneous squamous cell carcinoma. (A) Squamous cell carcinoma – well differentiated, 10x – Hematoxylin – Eosin; (B) Squamous cell carcinoma – moderately differentiated, 5x – Hematoxylin – Eosin; (C) Squamous cell carcinoma – poorly differentiated, 5x – Hematoxylin – Eosin.

Figure 2 presents the immunohistochemically profile of cSCC with positivity in the tumor cells for CK AE1/AE3 (A) and p40 (B and C)

Figure 3 presents the precursor lesions for cSCC: Bowen Disease (A and B) and Keratoacanthoma (C).

Discussion

cSCC, a NMSC, is one of the most common malignancies of the skin. According to the latest Globocan statistics, 1,198,073 new cases of NMSCs were diagnosed worldwide in 2020 and 63,731 deaths were caused by NMSCs. Basal cell carcinoma, cSCC, and basosquamous carcinoma ac-

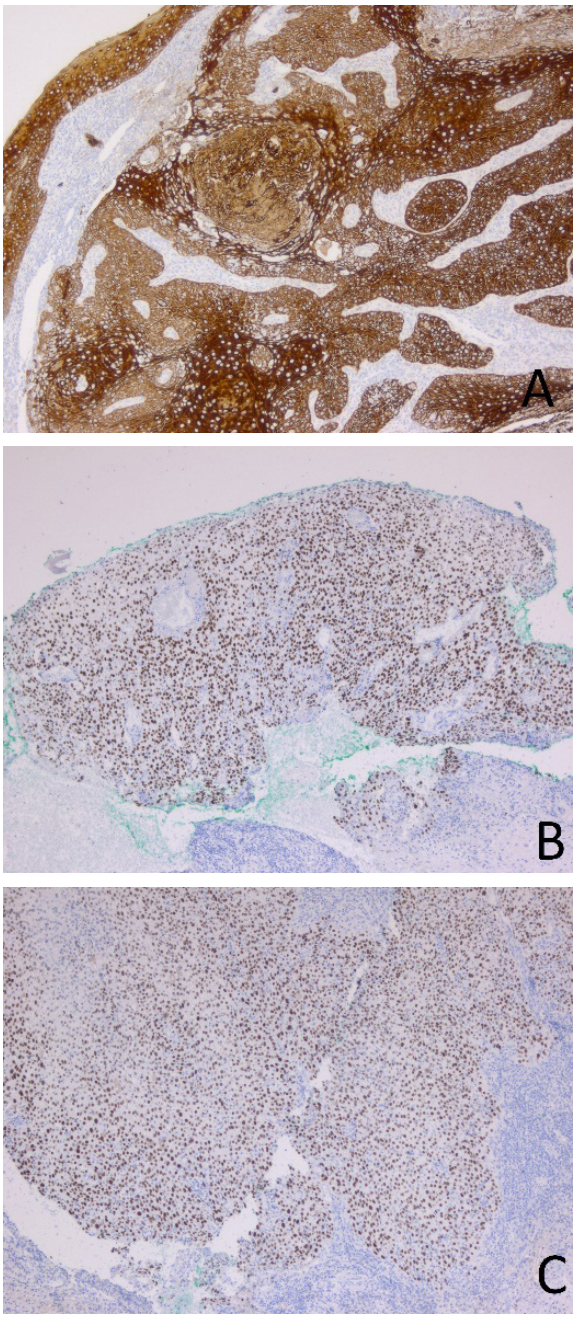

Fig. 2. Immunohistochemical profile of the cutaneous squamous cell carcinoma. (A) Squamous cell carcinoma, 10x – Immunohistochemistry – PanCK; (B) Squamous cell carcinoma, 5x – Immunohistochemistry – p40; (C) Squamous cell carcinoma, 10x – Immunohistochemistry – p40.

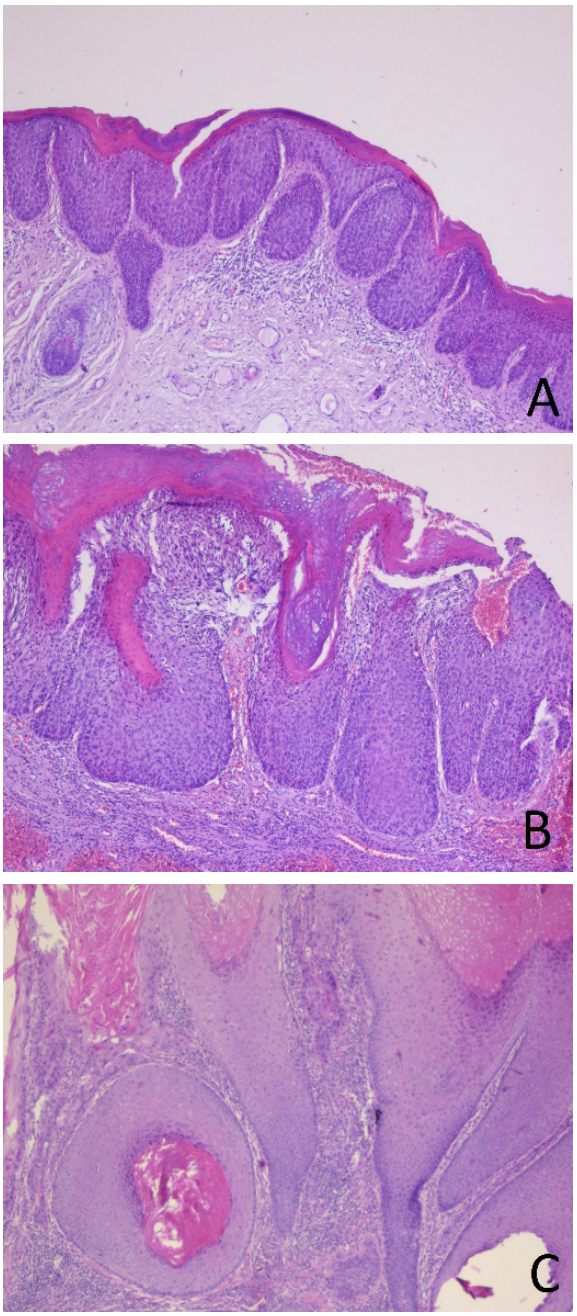

Fig. 3. Precursor lesions of the cutaneous squamous cell carcinoma. (A) Bowen disease (carcinoma in situ), 5x – Hematoxylin – Eosin; (B) Bowen disease (carcinoma in situ), 10x – Hematoxylin – Eosin; (C) Keratoacanthoma, 10x – Hematoxylin – Eosin.

count for most NMSCs; 20% of NMSCs are cSCCs [1, 2].

The first section of Table I details the number of cases of cSCC diagnosed in the Pathology Department during the study period. As can be seen, the number of diagnosed cases increased in 2018 and 2019 and then sharply decreased in 2020. The reduction in the number of diagnoses in 2020 was related to the COVID-19 pandemic, which limited the number of surgical procedures performed worldwide. As a result, patients with NMSCs are now presenting with more lesions at more advanced stages [8-10].

Table I also shows the ages of the patients diagnosed with cSCC during the study period. Most of the patients included in the study were over 70 years old (median age, 63.0 years). Fewer than 5% of the patients were less than 40 years old. Kreim et al. reported that the incidence of cSCC was higher in elderly people than younger individuals, especially in patients presenting over the last year [11, 12]. Men were more likely to develop cSCC than women, and most of the patients diagnosed with cSCC grew up in urban environments. Their vulnerability to cSCC may be due to prolonged exposure to radiation, other toxins, and UVA/UVB radiation [5,13,14]. Most of the tissue samples were provided from the Plastic and Reconstructive Surgery and General Surgery wards. Advanced surgeries for skin tu-

mors, re-excisions, and excisions of large tumors are always performed in those wards as they offer the widest selection of intervention techniques.

Table II presents the histological parameters of the cases. Most of the 96 cases included in the study were cSCC, followed by keratoacanthoma (Figure 3C) and Bowen disease or carcinoma in situ (Figures 3A and 3B). Keratoacanthoma (Figure 1C) was identified as a malignant tumor in the most recent *WHO Classification of Skin Tumours* (disease code 8071/3). Patients with keratoacanthoma can develop cSCC [1, 11, 12].

The differentiation of cSCC is defined by the grade of the cytologic atypia and the degree of keratinization, (from visible keratin pearls in well-differentiated cSCC to little or no keratin in poorly differentiated cSCC). Most of the cases diagnosed with cSCC were well differentiated (Figure 1A), followed by moderately differentiated (Figure 1B) and poorly differentiated (Figure 1C) cases. The differential diagnosis between cSCC and other skin pathologies is important. In poorly differentiated cases, not only other NMSCs but also melanoma should be considered. Immunohistochemistry is a very useful ancillary test to establish the diagnosis of cSCC. Tumor cells in cSCC are usually positive for CK AE1/AE3 (Figure 2A), p40 (Figures 2B and 2C) and p53, but negative for BerEP4 and the melanocytic markers. This may distinguish them from other types of NMSCs, such as basal cell carcinoma, or melanocytic tumors such as melanoma [1, 5, 15, 16].

Most of the lesions were surgically removed within the surgical safety margins. Excision within the safety limits is a very important parameter because incomplete excision may lead to recurrence and metastasis. The capacity of cSCC, especially poorly differentiated cSCC, to metastasize is well known [1, 15].

The COVID-19 pandemic delayed many histopathological diagnoses of cSCC. Patients feared visiting hospitals, and healthcare resources were diverted to the treatment of COVID-19 [8, 9, 10]. These factors led to diagnoses at more advanced stages and worse patient outcomes.

Conclusion

cSCC remains one of the most frequently diagnosed malignant skin cancers. In our study, most of the patients diagnosed with cSCC presented in 2018 and 2019, were male, were more than 70 years old, and grew up in urban environments. Special attention should be given to precursor lesions such as keratoacanthoma and Bowen disease. Even though most of the cases were well differentiated and completely excised surgically, the differential diagnosis between cSCC and other skin malignancies, determined with the help of an immunohistochemical profile, was important in identifying the correct treatment.

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Authors contributions

IGC: conception and design, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be published

MCP and AHS: revising the article, acquisition of data, analysis of data, final approval of the version to be published

AM and RN: drafting the article, interpretation of data, final approval of the version to be published

OSC: conception and design, acquisition of data, drafting the article, final approval of the version to be published

Conflict of interest

None to declare.

References

1. Elder DE, Massi D, Scolyer RA, Rein Willemze, Cancer L, Al E. WHO classification of skin tumours [Internet]. Lyon: International Agency For Research On Cancer; 2018. Available from: https://publications.iarc.fr/Book-And-Report-Series/Who-Iarc-Classification-Of-Tumours/WHO-Classification-Of-Skin-Tumours-2018
2. Heppt MV, Leiter U. Cutaneous squamous cell carcinoma: state of the art, perspectives and unmet needs. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology: JDDG [Internet]. 2023 Apr 1 [cited 2023 Aug 8];21(4):421–4. Available from: https://pubmed.ncbi.nlm.nih.gov/36999577/
3. 2020 G. Non-melanoma skin cancer [Internet]. 2020. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/17-Non-melanoma-skin-cancer-fact-sheet.pdf
4. Zhang Y, Guo Z, Wang H, Li B. Global status of research on cutaneous squamous cell carcinoma and its programmed cell death: Bibliometric and visual analysis from 2012 to middle 2022. Frontiers in Oncology. 2023 Apr 11;13.
5. Fania L, Didona D, Di Pietro FR, Verkhovskaia S, Morese R, Paolino G, et al. Cutaneous Squamous Cell Carcinoma: From Pathophysiology to Novel Therapeutic Approaches. Biomedicines. 2021 Feb 9;9(2):171.
6. Mannino M, Piccerillo A, Dika E, Vaccari S, Quaglino P, Rubatto M, et al. Advanced Cutaneous Squamous Cell Carcinoma: Italian Multicentric Retrospective Analysis of Patient Profiles and Therapeutic Approaches. Dermatology. 2023 Jan 1;239(3):422–8.
7. Schmitz L, Kanitakis J. Histological classification of cutaneous squamous cell carcinomas with different severity. Journal of the European Academy of Dermatology and Venereology. 2019 Dec;33(S8):11–5.
8. Marko Jović, Milana Marinković, Branko Suđecki, Milana Jurišić, Zoran Bukumiric, Jovanovic M, et al. COVID-19 and Cutaneous Squamous Cell Carcinoma—Impact of the Pandemic on Unequal Access to Healthcare. Healthcare. 2023 Jul 10;11(14):1994–4.
9. Cocuz IG, Cocuz ME, Niculescu R, Șincu MC, Tinca AC, Sabău AH, et al. The Impact of and Adaptations Due to the COVID-19 Pandemic on the Histopathological Diagnosis of Skin Pathologies, Including Non-Melanocyte and Melanoma Skin Cancers—A Single-Center Study in Romania. Medicina. 2021 May 27;57(6):533.
10. Cocuz IG, Cocuz ME, Repanovici A, Sabău AH, Niculescu R, Tinca AC, et al. Scientific Research Directions on the Histopathology and Immunohistochemistry of the Cutaneous Squamous Cell Carcinoma: A Scientometric Study. Medicina. 2022 Oct 13;58(10):1449.
11. Green AC, Olsen CM. Cutaneous squamous cell carcinoma: an epidemiological review. British Journal of Dermatology. 2017 Feb 16;177(2):373–81.
12. Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma. Journal of the American Academy of Dermatology. 2018 Feb;78(2):237–47.
13. Kim Y, Feng J, Su KA, Asgari MM. Sex-based differences in the anatomic

distribution of cutaneous squamous cell carcinoma. International Journal of Women's Dermatology [Internet]. 2020 May 27 [cited 2022 Nov 25];6(4):286–9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7522808/

14. Molina BD, M.G. Crespo Leiro, Luis Alonso Pulpón, Mirabet S, J.F. Yañez, Bonet LA, et al. Incidence and Risk Factors for Nonmelanoma Skin Cancer After Heart Transplantation. Transplantation Proceedings. 2010 Oct 1;42(8):3001–5.
15. Bălășescu E, Gheorghe AC, Moroianu A, Turcu G, Brînzea A, Antohe M, et al. Role of immunohistochemistry in the diagnosis and staging of cutaneous squamouscell carcinomas (Review). Experimental and Therapeutic Medicine. 2022 Apr 11;23(6).
16. Lobl M, Grinnell M, Phillips A, Abels J, Wysong A. The Correlation Between Immunohistochemistry Findings and Metastasis in Squamous Cell Carcinoma. Dermatologic Surgery. 2020 Nov 3;Publish Ahead of Print.