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Expression of Cancer Stem Cell Markers CD133 and Nestin in Skin Tumors in Egyptian Patients

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Abstract

Background: Skin tumors represent 4.78% of primary malignant tumors in Egyptian patients. Among the common skin tumors in Egyptian patients; are invasive keratinocytic/ epidermal tumors, constitutes 78.5% of primary skin tumors. Cancer stem cells (CSCs) are a population of cells responsible for tumor initiation, cancer progression and therapeutic resistance in manycancers. The CD133 protein is a transmembrane glycoproteinthat has been considered a putative and important CSC biomarker in various tumors, including gastric, breast, and colon tumors. Nestin is an intermediate filament protein that was described as a marker of neural progenitor cells during development of the central nervous system. In tumors, nestin expression is reported in malignancies of various tissues, and high levels have been correlated with aggressive features in brain tumors, non-small cell lung cancer and breast cancer.

Aim of Study: To study the immunohistochemical expression of stem cell markers; CD133 and nestin in some skin tumors, to evaluate the relation of their expression with other histopathologic features and other predictor parameters in these tumors.

Material and Methods: The immunohistochemical expression of CD 133 and nestin were assessed in 44 cases of keratinocytic/epidermal tumors (20 cases of squamous cell carcinoma, 20 cases of basal cell carcinoma and 4 cases of trichoblastoma), which were collected from the surgical pathology files of the histopathology department, Al-Azhar University Hospitals during the period 2018-2020. Three sections of normal skin were also included in the study to assess for the immunohistochemical expression in normal structures.

Results: All cases of normal skin included showed negative immunostaining for nestin and CD133. Except for a limited nestin expression related to hair follicles. Nestin was expressed in 14 out of the 20 cases of squamous cell carcinoma (70.0%) with a statistically significant direct relationship between nestin expression and tumor size (P-value 0.015), and tumor grade (*p*-value 0.04). Nestin was not expressed in any of the 20 cases of basal cell carcinoma or 4 cases of trichoblastoma examined. CD133 was not expressed in any of squamous cell carcinoma, basal cell carcinoma or trichoblastoma cases examined.

Conclusion: Cancer stem cell markers; nestin and CD133 are not expressed in normal skin with exception of limited nestin expression related to hair follicles, a findings that suggest a role of both markers related more to neoplastic process rather than normal physiological processes. Nestin was expressed in squamous cell carcinoma with statistically significant relationship with tumor size (measured by maximal tumor dimension) and tumor grade. This may explain in part the aggressive behaviour of some high-grade squamous cell carcinoma cases. Nestin was not expressed in basal cell carcinoma; which may indicate different cellular origin and may explain the indulant locally malignant behaviour of such tumors.

Key Words: *CD133 – Nestin – Squamous cell carcinoma – Basal cell carcinoma – Trichoblastoma – Cancer stem cells.*

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Introduction

STEM cells generate great interest because they hold the promise for treatment of various incurable diseases. Several distinct stem cell populations have been identified in each organ, including the skin **[1]**.

Because of its enormous regenerative capacity and easy accessibility, skin has been the target of multiple stem cell studies **[2]**.

Cancer stem cells (CSCs) are a population of cells responsible for tumor initiation, cancer progression and therapeutic resistance in many cancers **[3]**. They are similar to stem cells in their ability of both self-renewal and differentiation into all cell types within a tumor **[4,5,6]**.

Skin tumors represent 4.78% of primary malignant tumors in Egyptian patients. Among the common skin tumors in Egyptian patients, are invasive keratinocytic/epidermal tumors which constitutes 78.5% of primary skin tumors, including basal cell carcinoma (54.6%) and squamous cell carcinoma (44.9%) **[7]**.

CD133 protein, also known as human prominin-1, is a transmembrane glycoprotein [8] that has been considered a putative and important CSC biomarker in various tumors including gastric [9], breast [10], and colon tumors [11].

Nestin is an intermediate filament protein that was first described as a marker of neural progenitor cells during development of the central nervous system [12].

In tumors, nestinexpression was reported in malignancies of various tissues, and high levels have been correlated with aggressive features in brain tumors [13,14], non-small cell lung cancer, [15], breast cancer [14], gastrointestinal stromal tumors (GIST) [16] and angiosarcoma [17].

Additionally, nestin has been suggested as a marker of tumor angiogenesis in cancers such as prostate [18], breast [19] and colorectal cancer [20].

The aim of this work was to study the immunohistochemical expression of stem cell markers; CD133 and nestin in some skin tumors, mainly non-melanocytic to evaluate the relation of their expression and their association with some clinical and pathological features.

Material and Methods

The material of this work consisted of 44 cases of skin tumors, which were collected from the surgical pathology files of the Histopathology Department, Al-Azhar University Hospitals during the period 2018-2020. The material included 20 cases of squamous cell carcinoma, 20 cases of basal cell carcinoma and 4 cases of trichoblastoma.

Three sections of normal skin were also included in the study to assess for the immunohistochemical expression in normal structures.

Patient data were retrieved from the pathology reports and included age, sex and different histopathological parameters e.g. tumor thickness, surface ulceration and size of the tumor.

Paraffin blocks were re-cut by rotatory microtome at 5 microns thickness then mounted on glass slides and were stained by hematoxlyin and eosin (H&E) for confirmatory histopathological diagnosis. Tumors were subtyped and graded according to WHO 2018 classification of skin tumors [21].

Immunohistochemical staining:

For immunohistochemical study, 4-5 micron thick sections were obtained on poly-l-lysine coated slides.

The primary antibody used for immunohistochemical staining, (with the clone, manufactures, dilution) was as follows; Anti-Nestin antibody [monoclonal ready to use antibody, SP103, Cambridge, MA 02139-1517 USA, at a dilution of 1/100] and Recombinant Anti-CD133 antibody [Anti-CD133 (Prominin-1) Antibody, clone 2F8, ZooMAb® Rabbit Monoclonal, Cambridge, MA 02139-1517 USA, ready-to-use]. Clone 2F8 is a ZooMAb rabbit recombinant monoclonal antibody that specifically targets an epitope with 77 amino acids from the N-terminal extracellular domain.

Immunohistochemical staining was performed in an autostainer (Dako autostainer link 48) using a polymer-based detection system (Dako En VisionTM FLEX, K8000). Diaminobenzidine (DAB) was used as chromogen and hematoxylin as counterstain.

Sections of normal renal tissue were used as a positive control for normal nestin expression [22]. Sections obtained from normal pancreatic tissue were used as a positive control for normal CD133 immunostaining in pancreatic acinar cells [23].

Negative controls were performed by omitting nestin and CD133 antibodies during the primary antibody incubation [24].

Assessment of nestin and CD133 immunostaining:

Cytoplasmic staining was considered positive for both nestin and CD133. The expression was correlated with different histopathologic prognostic parameters including tumor size, tumor grade and tumor thickness/depth.

Results

The study included 20 cases of squamous cell carcinoma, 20 cases of basal cell carcinoma and 4 cases of trichoblastoma.

Histopathological findings:

Squamous cell carcinoma (20 cases): Tumors were formed of nests and groups of malignant squamous cells with nuclear pleomorphism and variable keratinization (Fig. 1A,B). Two case of keratoacanthoma was included showing exo-endophytic growth pattern with a central horn-filled crater, surrounded by overhanging (lips) of epithelium. The sqouamous cells show abundant cytoplasm.

Different histopathological parameters of squamous cell carcinoma cases were summarized in (Table 1).

The mean tumor size assessed by the largest tumor dimension measured in millimetres was 11mm, ranging from 10mm to 50mm.

As regard tumor thickness (depth); the mean tumor thickness of included cases was 5.5mm, ranging from 3mm to 1 1mm.

Grouping of the tumor into histologic grades revealed that 8 cases were grade I (40%), 8 cases were grade II (40%) and 4 cases were grade III (20%).

Table (1): Histopathological parameters of squamous cell carcinoma cases.

	Squamous cell carcinoma group No.=20
Size:	
Median (IOR)	11 (3-20)
Range	10-50
Depth:	
Median (IOR)	5.50 (3-9)
Range	3-11
Grade:	
I	8 (40.0%)
II	8 (40.0%)
III	4 (20.0%)

1- *Basal cell carcinoma (20 cases):*

All the included cases of basal cell carcinoma were of the low-risk nodular type, formed of basaloid nodules with peripheral nuclear palisade. Epidermal attachment was evident in all cases. The stroma was fibromyxoid with cleft formation between the tumor nodules and the stroma (Fig. 1 C).

Different histopathological parameters of basal cell carcinoma cases were summarized in (Table 2).

The mean tumour size assessed by the largest tumor dimension measured by millimetres was 12.7mm, ranging from 7mm to 18mm.

As regards tumour thickness (depth), the median thickness of included cases was 7.4mm, ranging from 5mm to 10mm.

Table (2): Histopathological parameters of basal cell carcinoma cases.

	Basal cell carcinoma group No.=20
Size:	
Median (IOR)	12.7 (1.15-9)
Range	7-18
Thickness:	
Median (IOR)	7.4 (25-4.5)
Range	5-10
Type:	
Low risk	20 (100.0%)

3- *Trichoblastoma:*

Trichoepitheliomas were confined to the dermis. They were composed of islands of uniform basaloid cells, sometimes showing peripheral palisading. The stroma was cellular containing a wealth of fibrocytes associated with fibrillary collagen and was loosely arranged (Fig. 1D).

Immunohistochemical findings:

Nestin:

Normal skin and adnexa: All cases of normal skin included showed negative immunostaining for nestin. No immunoexpression was detected in the keratinocytes or melanocytes of normal skin biopsies included and skin adjacent to tumors. Adnexal structures were also negative (Fig. 3A).

Squamous cell carcinoma: Nestin was expressed in 14 out of the 20 cases of squamous cell carcinoma (70.0%). The staining pattern was cytoplasmic and diffuse (Fig. 2A,B). The staining intensity was strong in 12 cases, while moderate intensity was detected in two case of keratoacanthoma. (Fig. 2C). The other 6 cases were negative (30.0%) (Fig. 2D).

Relation between nestin expression and histopathological parameters of squamous cell carcinoma cases (Table 3).

Table (3): Relation between nestin expression and the histologic parameters of cases of squamous cell carcinoma.

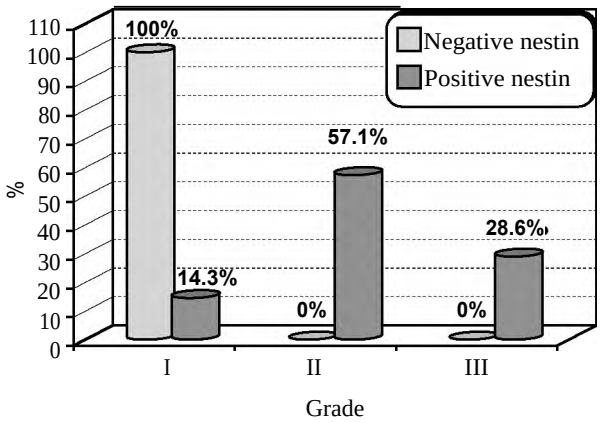
	Negative nestin No.=6	Positive nestin No.=14	Test value	*p*-value	Sig.
Size:					
Median (IOR)	12 (10-12)	20 (20-30)	–2.43 8#	0.015	S
Range	10-12	18-50)			
Depth:					
Median (IOR)	6 (3-11)	5 (3-9)	–0.464#	0.642	NS
Range	3-11)	3-9			
Grade:					
I	6 (100.0%)	2 (14.3%)	6.429*	0.04	S
II	0 (0.0%)	8 (57.1%)			
III	0 (0.0%)	4 (28.6%)			

p-value >0.05: Non significant. *: Chi-square test.
p-value <0.05: Significant. : Mann-Whitney test
p-value <0.01: Highly significant

When correlation was done between nestin expression and tumor size; a statistically significant direct relationship was found (*p*-value 0.015), thus immunoexpression of nestin was detected in cases with larger tumor size.

All positive cases had mean tumor size of 20mm, the mean size of negative cases was 12mm.

When correlation was done between nestin expression and tumor grade, a statistically significant direct relationship was found (*p*-value 0.04). Nestin was expressed in 14 cases out of 20 cases (2 case of grade I, 8 cases of grade II and 4 cases of grade III), while all negative cases (6 out of 10 cases) were of grade I. (Graph 1).



Graph (1): Relation between nestin results and tumor grade in squamous cell carcinoma.

When correlation was done between nestin expression and depth of tumotr infiltration and anatomical level of infiltration, no statistically significant relationship was found.

Basal cell carcinoma: Nestin was not expressed in any of the 20 cases of basal cell carcinoma examined (Fig. 3B). However; it was expressed in the endothelial cells of stromal vessels and in the tumor stroma in all included cases (Fig. 3C). The Peritumoral stroma and tumor-stroma interface (TSI) was positive for nestin in all cases included (Fig. 3D).

Trichoblastoma: Nestin was not expressed in the tumor cells of the two cases of trichoepithelioma studied.

CD133:

Normal skin and adnexa: All included cases of normal skin showed negative immunostaining for CD133.

Squamous cell carcinoma: CD133 was not expressed in any of the 20 cases of squamous cell carcinoma examined.

Basal cell carcinoma: CD133 was not expressed in any of the 20 cases of basal cell carcinoma examined.

Trichoblastoma: CD133 was not expressed in any of the 4 cases of adnexal tumors with follicular differentiation examined.

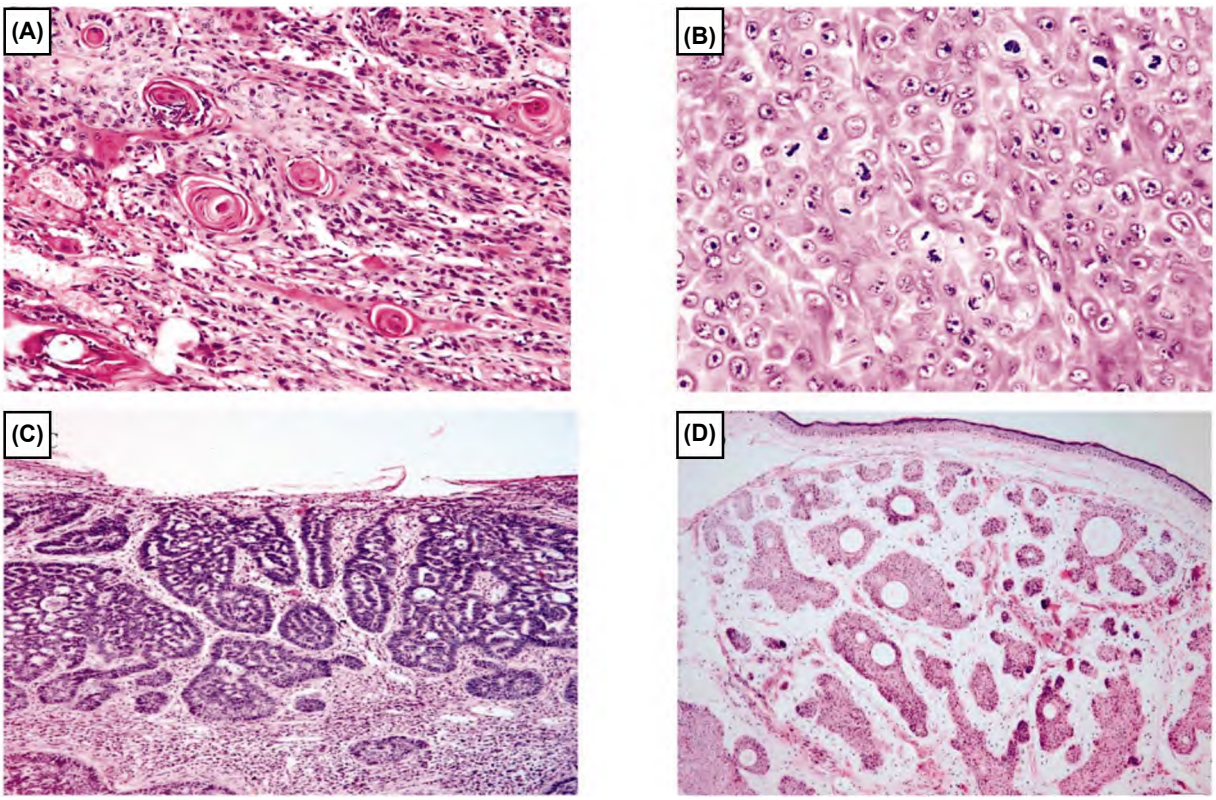


Fig. (1): (A): Squamous cell carcinoma, grade II, with keratin pearls formation (H&E x100). (B): Squamous cell carcinoma, grade III, with multiple mitotic figures (H&E x200). (C): Basal cell carcinoma, epidermal connection with ulceration and peripheral palisading (H&E x200). (D): Trichoblastoma, completely dermal tumor with no epidermal attachment (H&E x100).

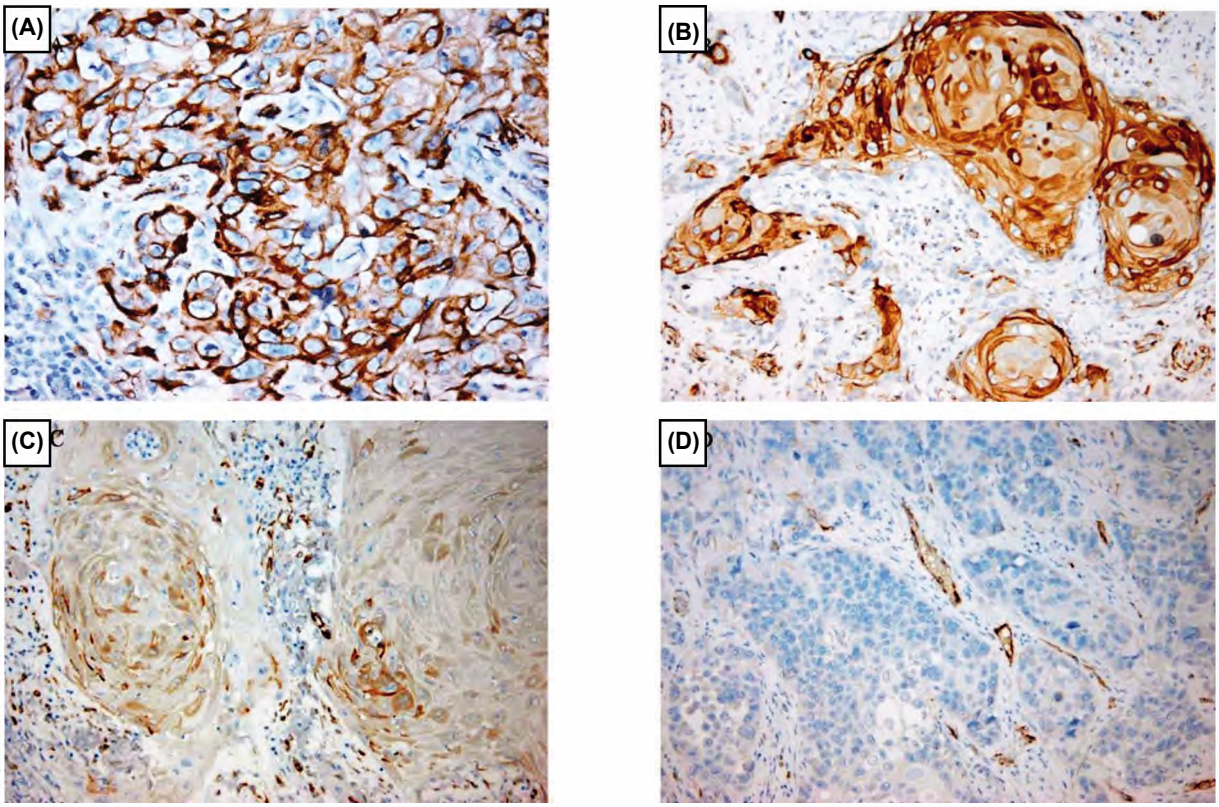


Fig. (2): (A): A case of squamous cell carcinoma with strong nestin immunostaining, cytoplasmic pattern (x200). (B): A case of squamous cell carcinoma with moderate immunostaing for nestin (x100). (C): A case of keratoacanthoma with weak immunostaig for nestin (x200). (D): A case of squamois cell carcinoma, with abscent immunoexpression of nestin (x 100).

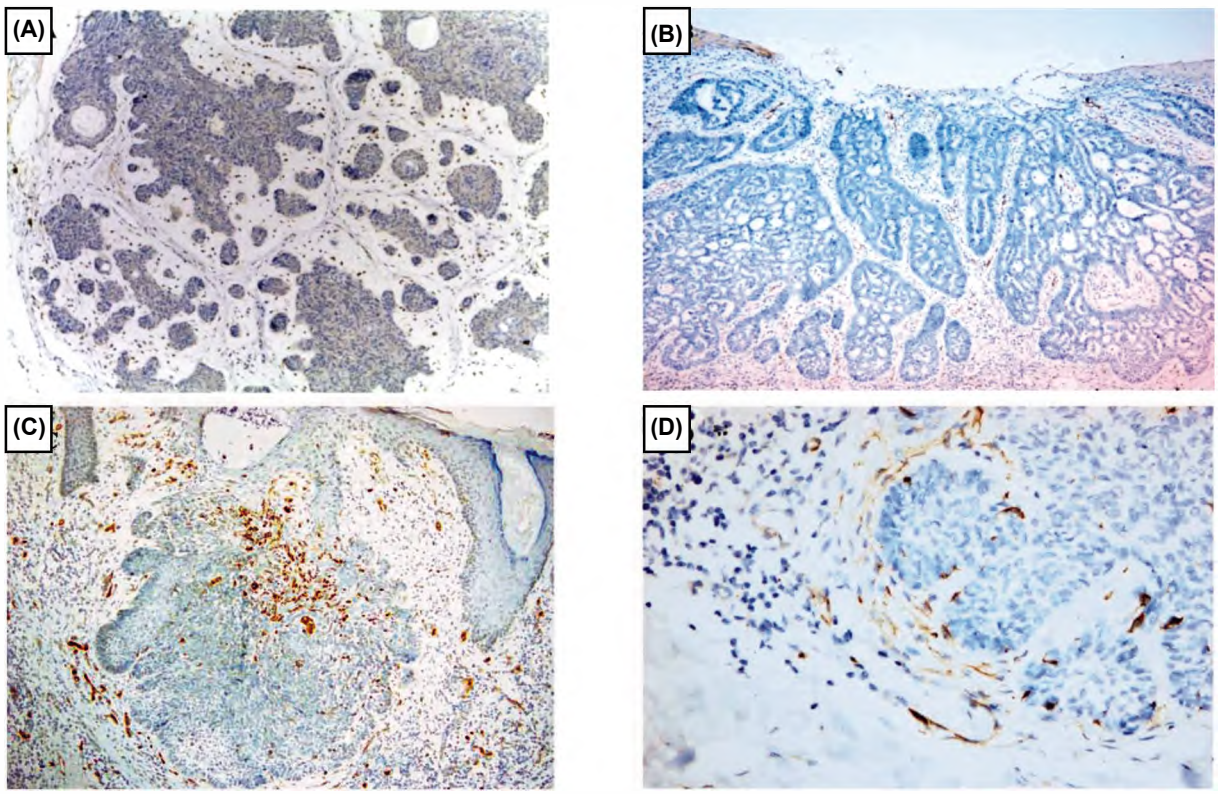


Fig. (3): (A): A case of trichoblastoma with abscent immunostaining for nestin (x100). (B): A case of basal cell carcinoma with abscent immunostaining for nestin (x100). (C): A case of basal cell carcinoma with positive tumor stromal immunostaing for nestin (x200). (D): A case of basal; cell carcinoma with enhanced stromal immunostaing at tumor stroma interface (x400).

Discussion

Cancer stem cells (CSCs) are a small population of the whole tumor cells and are the only cells that possess the ability to initiate and maintain tumor development [25]. The main reason for metastasis, relapse of tumors and resistance to general chemotherapy are related to these populations of cells [26]. Identification and characterization of these cells would be useful in cancer therapy [27,28].

Among several markers that have been identified for the characterization of cancer stem cells, CD133 and nestin are the most widely reported [29,30,31].

Kanoh et al., [32] have studied the expression of nestin in different compartments of normal skin. They observed the negative expression of nestin in epidermal cells and limited expression of nestin in hair follicles; being limited only to the inner root sheath of the area just beneath the sebaceous glands.

These findings are in line with the results of our study, hence both studies conclude that nestin is not expressed in normal epidermis and only focally expressed in normal hair follicles.

In this study, only nestin was expressed in 14 out of 20 cases of squamous cell carcinoma (SCC) (70%), while all basal cell carcinoma (BCC) and trichoblastoma cases were negative for nestin. All cases of SCC, BCC and trichoblastoma cases were negative for CD133.

Among the different clinicopathologic parameters studied in SCC cases; only tumor size (represented by largest tumor dimension) and tumor grade were proven to be statistically significant. Although a direct relationship was found between the depth of invasion and nestin expression; the results were statistically insignificant.

This finding is in line with what observed in the previous studies by Kanoh et al., [32], Abbas and Bahwan [33], and Rabea et al., [34].

Kanoh et al., [32] observed positive nestin expression in only three out of 16 cases of SCC (19%). This result is in line with those of Abbas et al., [33] who documented nestin expression in 9 out of 20 cases of SCC (45.5%).

Rabea et al., [34] investigated 23 cases of BCC and 22 cases of SCC, for expression of nestin. They demonstrated nestin expression in 10 out of 22 cases of SCC (45.5%) while only 3 out of 23 cases of basal cell carcinoma showed only a very weak immunostaining pattern. Both Kanoh et al., [32] and Abbas and Bahwan [33] reported negative immunostaining of BCC cases to nestin (0%) and both postulated that the different nestin-positive stem cell populations in the skin do not appear to play a role in BCC development and BCC tumor cells may arise from the more mature nestin negative/CD34-negative outer-root sheath cells [32,33].

The current study, interestingly; revealed more positive nestin expression in SCC cases (70%) than previous studies, which may be partially explained by the inclusion of grade III cases and a slightly larger tumor size relative to previous studies.

This relatively high percentage of SCC cases expressing nestin may reflect dedifferentiation towards a stem cell-like state that is uncommitted to terminal squamous differentiation which may require further studies to evaluate nestin expression in spindle cell squamous cell carcinomas [32].

In the study of Quist et al., [35], nestin was expressed in the stroma of some adnexal tumors e.g. trichoblastoma and in tumor stromal interaction (TSI) sites of malignant adnexal tumors e.g. sebaceous carcinoma. In the current study also this pattern of occasional stromal cells staining for nestin as well as in endothelial cells of tumor stromal blood vessels was observed only in basal cell carcinoma cases.

This pattern of stromal staining indicates an active role in reciprocal signalling between the tumour and the stroma cells [20].

Conclusion:

In conclusion, taken together, our findings revealed that Cancer stem cell markers; nestin and CD133 are not expressed in normal skin with exception of limited nestin expression related to hair follicles, and focal staining of normal endothelial cells lining dermal blood vessels, a findings that suggest a role of both markers related more to neoplastic process rather than normal physiological processes. Nestin was expressed in squamous cell carcinoma with statistically significant relationship with tumor size (measured by maximal tumor dimension) and tumor grade. This may explain in part the aggressive behaviour of some high-grade squamous cell carcinoma cases. Nestin was not expressed in basal cell carcinoma or trichoblastoma; which may indicate different cellular origin and may explain the indulant locally malignant behaviour of such tumors.

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تعبير دلالات خلايا السرطان الجذعية سى دى ١٣٣ ونستين فى أورم الجلد فى المرضى المصريين

خلفية البحث: تمثل أورام الجلد ٤.٧٨٪ من الأورام الخبيثة الأولية فى المرضى المصريين بشكل عام. من بين أورام الجلد الشائعة لدى المرضى المصريين، هى أورام الخلايا الكيراتينية المخترقة، وتشكل ٧٨.٥٪ من أورام الجلد الأولية، بما فى ذلك سرطان الخلايا القاعدية (٥٤.٦٪) وسرطان الخلايا الحرشفية (٤٤.٩٪).

الخلايا الجذعية السرطانية هى مجموعة من الخلايا المسؤولة عن بدء التورم وتطور السرطان، كما أن لها دور فى المقاومة العلاجية فى العديد من السرطانات.

يعد البروتين سى دى ١٣٣ جليكوبروتين عابر للغشاء الخلوى ويعتبر معلم حيوى إفتراضى عام للخلايا الجذعية السرطانية فى الأورام المختلفة، بما فى ذلك أورام المعدة والثدى والقولون. بالإضافة إلى ذلك، يرتبط تعبير البروتين سى دى ١٣٣ المرتفع بمآلات إكلينيكية سيئة فى بعض أنواع السرطان.

النستينبروتين خيطى وسيط تم وصفه على أنه معمل لخلايا العصبية الأولية أثناء تطور الجهاز العصبى المركزى. أما فى الأورام، فلقد تم رصد تعبير النستين فى الأورام الخبيثة فى الأنسجة المختلفة، وقد ارتبطت المستويات العالية بسمات عدوانية فى أورام المخ، وسرطان الرئة ذو الخلايا غير الصغيرة، وسرطان الثدى، والساركوما الوعائية.

الهدف من البحث: دراسة التعبير الهيسوكيميائى المناعى لواسمات الخلايا الجذعية السرطانية سى دى ١٣٣ والنستين فى بعض أورام الجلد، وتقييم علاقة تعبير هذه الواسمات مع السمات الباثولوجية النسيجية وغيرها من المعايير التنبؤية الأخرى فى هذه الأورام من أجل تشخيص وعلاج أفضل.

المواد وطرق البحث: تتكون مادة هذا العمل من ٤٤ حالة لأورام جلدية مختلفة تم جمعها من الملفات الجراحية لقسم الباثولوجى بمستشفيات جامعة الأزهر خلال الفترة من ٢٠١٨ إلى ٢٠٢٠. وقد اشتملت المادة على ٢٠ حالة من حالات سرطان الخلايا الحرشفية و٢٠ حالة من حالات من سرطان الخلايا القاعدية وأربع حالات من حالات الورم الأرومى المشعرى تم أيضاً تضمين ثلاثة مقاطع من الجلد الطبيعى فى الدراسة لتقييم التعبير الهيستوكيميائى المناعى فى البنية الطبيعية للجلد.

نتائج البحث: أظهرت جميع حالات الجلد الطبيعى المتضمنة فى الدراسة وجود اصطباغ سلبى لدالتى النستين والسى دى ١٣٣ حيث لم يحدث أى اصطباغ فى الخلايا الكيراتينية أو الخلايا الميلانية.

تم ملاحظة التعبير المناعى الهيستوكيميائى للنستين فى ١٤ من أصل ٢٠ حالة من حالات من سرطان الخلايا الحرشفية (٧٠.٠٪) بينما كانت الحالات الثلاث الأخرى سلبية (٣٠.٠٪).

وجدت علاقة مباشرة ذات دلالة إحصائية بين تعبير النستين وحجم الورم، ودرجته بينما أعطى عمق اختراق الورم للجلد علاقة غير ذات دلالة إحصائية.

لم يتم ملاحظة اصطباغ مناعى هيستوكيميائى فى أى من الحالات العشرين لسرطان الخلايا القاعدية التى تم فحصها. كما أنه لم يتم التعبير عنه فى أى من حالات الورم الأورمى المشعرى السبعة للواحق الجلد المضمنة بالرسالة.

لم يتم ملاحظة أى اصطباغ مناعى هيستوكيميائى للسى دى ١٣٣ فى أى من حالات سرطان الخلايا الحرشفية أو سرطان الخلايا القاعدية أو حالات الورم الأورمى المشعرى التى تم فحصها.

توصى الدراسة: بإجراء مزيد من الأبحاث حول العمليات الجزيئية التى تنظم تعبير النستين والسى دى ١٣٣ ويحدد إمكانية العلاج المستهدف المرتبط بهما فى الأورام الجلدية الخبيثة وتطوير استراتيجيات جديدة لعلاج سرطانات الجلد، وخاصة سرطانات الخلايا الحرشفية سيئة التمايز والتى تحتوى أورامهم على نسب أعلى من الخلايا الجذعية السرطانية موجبة التعبير للنستين والسى دى ١٣٣، وذلك بمصاحبة العلاج التقليدى أو بدونه.