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Stem Cell Marker OCT4 Expression and Its Clinicopathological Correlation in Squamous Cell Carcinoma of Cervix

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ABSTRACT

Background: Even now, cervical cancer weighs heavily on global health, especially in poorer nations, hitting women hard with illness and death. Though testing and treatment have improved, many still arrive at hospitals too late for effective care. Tumors can grow back or spread because some cells act like seeds - deep inside, they resist drugs and survive. These stubborn cells, called cancer stem cells, are thought to drive how disease moves forward. One protein, known as OCT4, helps keep such cells flexible and alive. Found active in several cancers, it shows up often in cervical tumors, raising interest among researchers watching its behavior.

Methods: A group of 56 tissue samples took part in this observation-based comparison - half came from people with cervical squamous cell cancer, the other half from those treated for long-term cervicitis. Preserved tissue slides were made, and testing was done with OCT4 to evaluate its levels.

Results: The results show that compared to the controls, the carcinoma samples had much higher levels of OCT4 (every cancer tested had some level of signal, while only 2/3rd of the controls had OCT4), and the difference was very highly significant (less than 0.001). In addition, the non-keratinized tumors had greater amounts of OCT4 than the keratinized tumors (0.013); there was a greater increase in the number of OCT4 based on the loss of differentiation; the OCT4 activity increased continuously from well-differentiated to poorly differentiated (p=0.040).

Conclusion: Cervical squamous cell cancer has been found to have a strong correlation to OCT4 levels, which might be indicative of the tumor's aggressiveness. The presence of this biomarker could eliminate the uncertainty regarding tumor stage and help direct the course of treatment. Furthermore, if this trend continues over time, treatment decisions may change as a result.

KEYWORDS: *Cervical Squamous Cell Carcinoma, Clinicopathological Correlation, Immunohistochemistry, OCT4 Expression, Stem Cell Marker.*

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INTRODUCTION

Cervical Cancer is still recognized as a major health burden and represents one of the frequently diagnosed cancers among women internationally including india.1,2 However, despite improvements in screening programs and vaccination strategies, a considerable number of cases of cervical cancer are still diagnosed at advanced stages, which has a substantial effect on surviving with cervical cancer and on quality of life for patients.3,4 A combination of high-risk Human Papillomavirus (HPV) infection, socioeconomic position, immune response, genetic predisposition and environmental factors are believed to contribute to the development of cervical cancer.5,6 Heterogeneity of tumors, which has increasingly been shown to be a contributing factor to variability in tumor behaviour and treatment response, has also been linked to the presence of cancer stem cells (CSCs).7 Cancer stem cells may be defined as a distinct subpopulation of tumor cells that have the ability to self-renew and differentiate and sustain tumor growth.8,9 CSCs play an important role in the development of cervical cancer through both tumor initiation and tumor metastasis and contribute to resistance to conventional therapies for the treatment of cervical cancer. CSCs have been identified in numerous cancer types, namely breast, prostate and colorectal cancers,10-12 and their role in advancement of cervical cancer is becoming increasingly evident.13,16

Among various CSC markers, OCT4 (octamer-binding transcription factor 4) has emerged as a critical regulator of stem cell pluripotency and self-renewal.14 It is normally present in embryonic stem cells and in several malignancies. Elevated OCT4 expression has been linked to resistance to radiotherapy

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and chemotherapy.15 The present study was done to evaluate the expression of OCT4 in cervical squamous cell carcinoma and to correlate it with clinicopathological parameters.

MATERIALS AND METHODS

A two-year observation began in January 2019, wrapping up by January 2021, hosted at Era Lucknow Medical College and Hospital. Ethical clearance came through committee endorsement (EC/2019/118) before any steps were taken. Each participant signed only after fully understanding what would happen. Fifty-six samples made up the research group - half showed cervical squamous cell carcinoma, proven through tissue analysis, while the other half had chronic cervicitis, used for comparison. Fresh diagnoses with no earlier care shaped the cancer portion, keeping past treatments from clouding results.20 The presence of brown nuclear staining in tumor cells was considered indicative of positive expression.17,18 Staining intensity and distribution were assessed, and the score was calculated. The expression of OCT4 was assessed in relation to age, parity, clinicopathological stage, clinicopathological subtype, and tumor grade. Data was interpreted using SPSS version 21 & p-value of less than 0.05 was considered statistically significant.

RESULTS

The demographic and clinical profile of the study participants is presented in Table 1. A significantly higher proportion of older patients was observed in the malignant group compared to the non-malignant group ($p = 0.007$). Most participants in both groups were married. Although a greater number of children was more commonly noted among patients with malignancy, the association was not statistically significant ($p = 0.660$). Stage II was found to be where the majority of diagnosed cancers occurred, with stages III, I and IV following closely behind (stages I and II together made up 81%). This suggests that patients with cancer at the time of diagnosis appeared to have an advanced disease stage.

Keratinizing squamous cell carcinoma has been determined to be the most frequent histopathological cancer type which was present in more than 70% of all cancer cases reviewed. All non-keratinizing squamous cell carcinoma accounted for nearly 30% of all patients studied; these subtypes have therefore been classified as non-keratinizing SCC. Table 1 demonstrates that OCT4 expression was significantly higher in cervical cancer tissues as against non-neoplastic samples. In all instances of cervical carcinomas, there was positive OCT4 expression, but the number of cases that showed positivity in chronic cervicitis was small. This change was statistically highly pronounced ($p < 0.001$).

The association between OCT4 immunohistological scores and various clinicopathological parameters is presented in (Table 2). Mean OCT4 scores were significantly higher in non-keratinizing squamous cell carcinoma compared to keratinizing subtype ($p = 0.013$), suggesting a possible association with more aggressive tumor behavior.

Furthermore, an increasing trend in OCT4 expression was observed with tumor grade. Poorly differentiated tumors exhibited higher expression levels in comparison with

Table 1: General characteristics and demographic profile of cases and controls.

SN	Characteristic	Cases (n =28)	Controls (n=28)	Statistical significance
1	Mean age ± SD (range) in years	49.82 ± 11.98 (25–70)	41.29 ± 10.69 (23–60)	$t = 2.812$; $p = 0.007$
2	Marital status			
	Married	28 (100%)	28 (100%)	—
3	Mean parity ± SD	4.18 ± 2.07	3.93 ± 2.16	$t = 0.442$; $p = 0.660$
4	Clinical stage (cases only)			
	Stage I	4 (14.3%)	—	—
	Stage II	15 (53.6%)	—	—
	Stage III	7 (25.0%)	—	—
	Stage IV	2 (7.1%)	—	—
5	Histopathological diagnosis			
	Keratinizing SCC	20 (71.4%)	—	—
	Non-keratinizing SCC	8 (28.7%)	—	—
	Chronic cervicitis	—	28 (100%)	$\chi^2 = 56.00$; $p < 0.001$
6	Histopathological grade (cases only)			
	Well differentiated	6 (21.4%)	—	—
	Moderately differentiated	14 (50.0%)	—	—
	Poorly differentiated	8 (28.6%)	—	—
7	**OCT4 expression**	**28 (100%)**	**7 (32.1%)**	**$\chi^2 = 33.6$; $p < 0.001$**

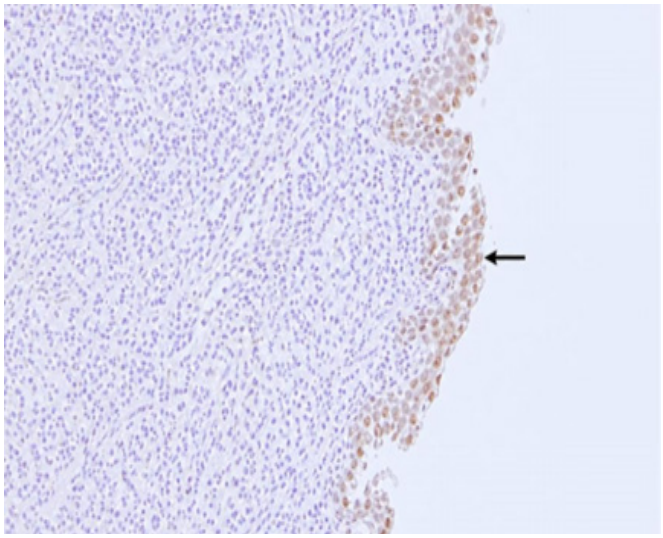
moderately and well-differentiated tumors,such a trend was statistically significant (p = 0.040) (Table 2).

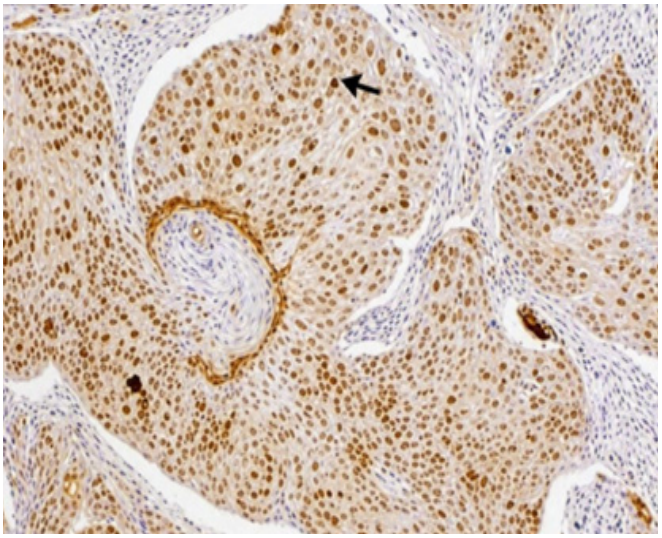
However, no significant association was observed between OCT4 expression and other clinicopathological parameters such as age, parity, or clinical stage.

Representative photomicrographs demonstrating OCT4 immunoexpression in cervical tissues are shown in (Figure 1). These images illustrate weak nuclear positivity in chronic cervicitis and progressively stronger nuclear staining in well-differentiated, moderately differentiated, and poorly differentiated SCC.

Table 2: Association of OCT4 mean immunohistological scores with clinicopathological parameters in cases (n=28).

SN	Characteristic	Category	Mean score ± SD	Statistical significance
1	Age	≤45 years (n=14)	7.00 ± 2.88	z = 0.191; p = 0.874
		>45 years (n=14)	7.07 ± 2.37	—
2	Parity	<4 (n=18)	6.83 ± 2.60	z = 0.672; p = 0.524
		≥4 (n=10)	7.40 ± 2.68	—
3	Clinical stage	I (n=4)	6.25 ± 2.36	H = 5.595; p = 0.133
		II (n=15)	6.53 ± 2.00	—
		III (n=7)	7.14 ± 2.97	—
		IV (n=2)	12.00 ± 0.00	—
4	Histopathological diagnosis	Keratinizing SCC (n=20)	6.25 ± 2.38	z = 2.535; p = 0.013
		Non-keratinizing SCC (n=8)	9.00 ± 2.07	—
5	Histopathological grade	WD (n=6)	6.17 ± 1.60	H = 6.445; p = 0.040
		MD (n=14)	6.29 ± 2.70	—
		PD (n=8)	7.04 ± 2.59	—





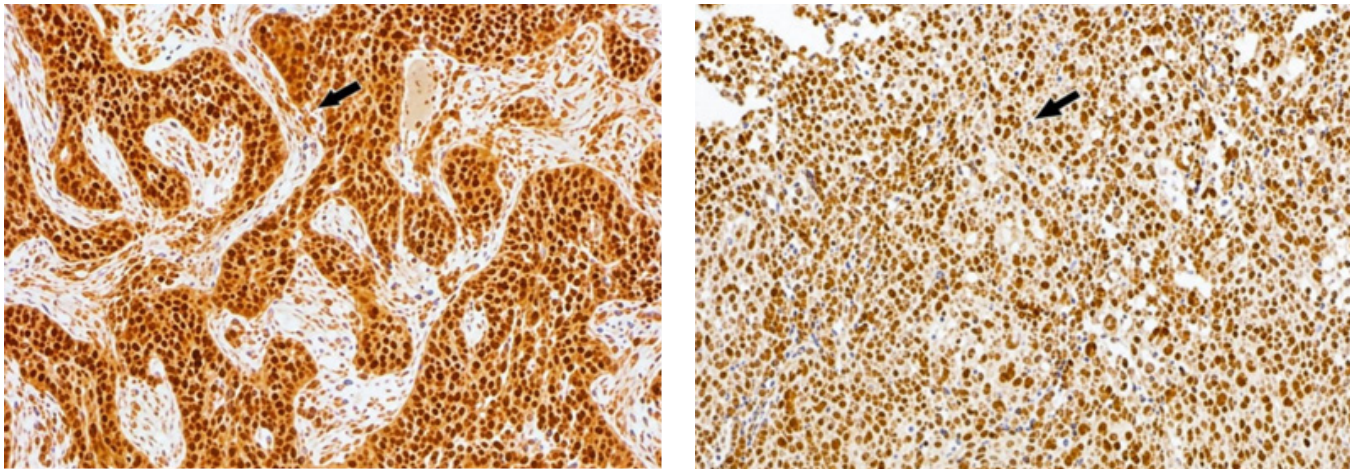


Figure 1: Photomicrograph showing OCT4 expression. (1A) Weak Nuclear positivity in chronic cervicitis (1B) Nuclear positivity in Well Differentiated SCC. (1C) Strong Nuclear immuno reactivity in Moderately Differentiated SCC. (1D) Strong Nuclear immunoreactivity in Poorly Differentiated SCC (IHC for OCT4,100X & 400X).

DISCUSSION

One of the main health threats to the world's population is cervical cancer, which remains a significant issue especially in underdeveloped countries where access to healthcare remains limited.[1,2] Having a later diagnosis makes an already narrow window of treatment options even more difficult due to limitations on when they can be treated. For those that have reached an advanced stage, there will not be many effective ways to treat them.Recently, researchers have shifted their focus in cancer research to studying cancer stem cells – the unique group of cells from which cancers grow, develop, and spread; and the cells that escape conventional cancer treatments.[7–9] Therefore, identifying and developing reliable markers of these cells is critical to developing more accurate diagnosis and treatment plans. OCT4 is a marker found within cells that helps those cells maintain their "stem" function (i.e., retaining their ability to become any type of cell) – the research data shows there is definitely a relationship between high levels of OCT4 in tumour tissue, more rapid metastasis, and poorer prognosis among patients with tumours having high levels of OCT4.[17,18]

The data indicated that OCT4 level was significantly higher in samples of squamous cell cervical cancers than in corresponding samples of normal cervixes and had a distinct correlation to tumour growth. Upon evaluation of all specimens of squamous cell cervical cancer, there was a positive association between the presence of OCT4 protein and the ability to identify the presence of squamous cell cervical cancer. Specifically, the amount of OCT4 in the specimens from patients with non-keratinocytes squamous cell carcinoma (SCC) was significantly greater than the amount of the same protein in normal specimens, suggesting that OCT4 may play a role in driving more aggressive characteristics associated with various types of SCCs, including those found in the cervix. Previous studies also confirmed this relationship between OCT4 and the transition of normal cells to a transformed or aggressive phenotype.[18,25–30] In addition, the amount of OCT4 in tumours sorts out and increases as the tumour grade increases, further supporting the notion that it may also help facilitate the growth of cervical cancer. Tumours that do not develop well-defined architectures or structures are also typically associated with less favourable patient outcomes, and the identification of higher amounts of OCT4 in those tumours may provide an indication of the aggressiveness of the disease.

However, while OCT4 can be associated with the presence of cervical cancer tumours, this expression does not have any clear statistically significant relationship to the extent to which cervical cancer has metastasized in patients, the patients' age or the patients' parity (the number of children they have borne). This indicates that OCT4 may also be related to how cervical cancer tumours behave; however, there is insufficient evidence to co-join OCT4 with every reported patient-related variable in this study.

CONCLUSION

OCT4 levels often increase in cervical squamous cell carcinoma when looking at cancer cells. Aggressive tissues - particularly those lacking keratin or a defined structure - indicate a high concentration of OCT4. Furthermore, high levels of OCT4 correlates with poorer disease progression. Also, higher amounts of OCT4 point to an increased likelihood of being part of the rapid growth patterns associated with cancer.

Therefore, while it is possible that high levels of OCT4 may indicate aggressiveness and/or provide insight into the behavior of the cancer, further investigation on a larger scale is necessary before any conclusions can be made regarding OCT4 as a predictive marker or treatment target.

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