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Key Priorities For Immunohistochemical Testing In Predicting Cervical Cancer Recurrence

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ABSTRACT

Cervical cancer is an urgent problem due to its high morbidity, its growth tendency in women of reproductive age, and late presentation. As a result of insufficiently effective surgical and/or radiation treatment of the primary tumor, local recurrences occur in 10-40% of treated patients, and distant metastases in 35% of patients [10]. The first place according to the frequency of distant metastasis in RCC patients is occupied by para-aortic lymph nodes (31.2%), the second - lungs (16.1%), the third - bones (12.9%) [9]. Treatment of recurrent and generalized cervical cancer is a complex and unresolved problem of modern oncology due to the extremely limited range of possible therapeutic measures. The leading role in conservative therapy of cervical cancer relapses and metastases is played by highly toxic, but not specific cytostatics, which aggravates the condition of patients and the immunological failure of the organism [11].

KEYWORDS

Cervical cancer, marker recurrence, SD-3, SD20, biopsy, retrospective study.

INTRODUCTION

A retrospective study in 67 patients diagnosed with cervical cancer was carried out in this article and the effect of lymphoid infiltration in biopsy specimens was studied. Using immunohistochemical studies, where SD 3 and SD 20 were the main markers, differences in immune cell density and hence cellular immune response between patients with and

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without cervical cancer recurrence were identified. The problems of cervical cancer recurrence are due to the high rate of the disease and its recurrence in the first two years after completion of treatment. According to the World Health Organization, there are 528,000 new cervical cancer (CRC) cases and 266,000 cervical cancer deaths worldwide every year. High incidence of the disease is observed in developing countries, accounting for 78% of cases, In European region epidemiological data on incidence rates of cervical cancer show significant country differences: from 3.8 per 100,000 women in Switzerland to 25.0 per 100,000 women in Latvia. Despite treatment of metastatic lesion, prognosis of patients with recurrent and metastatic cancer is extremely unfavorable: only 10-15% of patients survive up to one year after their appearance. Therefore, the study and possibility of prognosis of cervical cancer and its recurrence is of great importance [6,14]. Immune surveillance is an important prerequisite for distant invasion and metastasis of tumor cells. Various solid tumors are reported to be infiltrated with a large number of lymphocytes, which correlates positively with the prognosis of patients . Although tumor tissues are infiltrated with large numbers of immune cells, it is still difficult to prevent invasion and metastasis of tumor cells, suggesting that tumor cells may escape observation and destruction by immune cells. It has also been found that tumor cells can induce differentiation of immune cells [7,13], such as TAM2 and Tregs macrophages [5,14]. Consequently, further understanding of the interaction between tumor cells and immune cells gives us an opportunity to screen new targets. It should be noted that an in-depth study of phenotypic and functional changes of immune cells in tumor tissues is essential for understanding and predicting recurrence. Cervical cancer has been found to have increased morbidity and mortality in women worldwide. Despite comprehensive treatment according to stratification, up to 40% of patients are at risk of recurrence [1]. Moreover, even new and promising therapies to prevent relapse have protective effects only in special categories of patients [2,12].

To date, there are several well-known prognostic factors (clinical stage, lymph node status, tumor size and depth of invasion, bcl-2, p53, KI-67, VEGF), but they do not always indicate an increased risk of cervical cancer patients recurrence. Despite recent advances in the immune mechanisms of cervical cancer (CRC), recurrence is still a pressing issue, and recognition of new prognostic biomarkers is essential. Since the immune response to cancer is considered an important parameter, evaluation of the local cellular immune response is crucial for the selection of patients who may need to develop new adjuvant treatment regimens including immunotherapy in the future [2, 3].

Obtaining thorough and detailed information about tumor-associated lymphocytes, the state of which is responsible for the cellular immune system in patients with relapsed cervical cancer, is an urgent goal. Various subsets of immune cells, mainly. T-cells and B-cells in biopsy samples showed some contradictory data, most authors come to the opinion that intra- and peritumoral infiltration of immune cells is associated with improved clinical outcome in cancer patients [4].

Purpose of study: Study of cellular immune response using DM 20 and DM 3 markers for early prognosis of cervical cancer recurrence

MATERIALS AND METHODS

We conducted a retrospective study in 67 patients diagnosed with cervical cancer with

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T1bNxMo-T2bNxMo stages, who received comprehensive treatment in the conditions of the Republican Specialized Scientific and Practical Medical Center and its Samarkand regional branch during the period 2010-2017. The patients were retrospectively divided into 2 comparison groups. Group 1 with relapse n=36 (54.3%), Group 2 without relapse n=31 (45.6%). The mean age was 46.4 ± 5.53 years. Baseline information was obtained from the following sources: objective status data at the time of examination and treatment, analysis of outpatient records, case histories, operative log, archival data, and the main study was pathomorphological laboratory data. Data of dynamic observation, interview of patients, inquiries to oncologic dispensaries and oncologic offices. Immunohistochemical examination (IHC) of the operative material was performed on serial paraffin sections in the laboratory: Premium Diagnostics LLC, 618A Uygur Street, Uchtepa district, Tashkent. To identify the immune cells of interest, specific antigens expressed on the cell surface were detected using IHC, assuming that tissue antigen identification is possible with appropriate antibodies. The primary antibodies (DAKO) used were mouse anti-human monoclonal antibodies; CD3 is a pan-T-cell marker, CD20 is expressed on mature B-cells. The characteristic T-cell antigen is CD3, and the B-cell marker is CD20, which is a non-glycosylated phosphoprotein expressed on the membrane of mature B cells. The simultaneous balanced interaction of T- and B-cell local immune response is important.

IHC was performed by flow cytofluorimetry on a Becton Dickinson analyzer. The index was calculated using the formula CD3+/CD20+. The results were expressed as a percentage of the total number of lymphocytes.

The density of the immune cell profile was further scored between "0" and "3" were assigned as: "0" indicated no lymphoid infiltrate, "1+" low, "2+" intense, and "3+" intense infiltrate with lymphoid follicles. Statistica 8.0 applied software package (StatSoft, USA) and SPSS Statistics 17.0 (USA) were used for statistical analysis. Results with a p value <0.05 were considered statistically significant. In some cases, the 95% confidence interval (CI 95%) was calculated and used to determine the reliability of the results.

RESULTS

The study results showed wide variability among tumors in the number of CD3+ T cells (median: 214.00 (0-999), CD20+B cells (29.50 (0-1152) per 1 mm^2.

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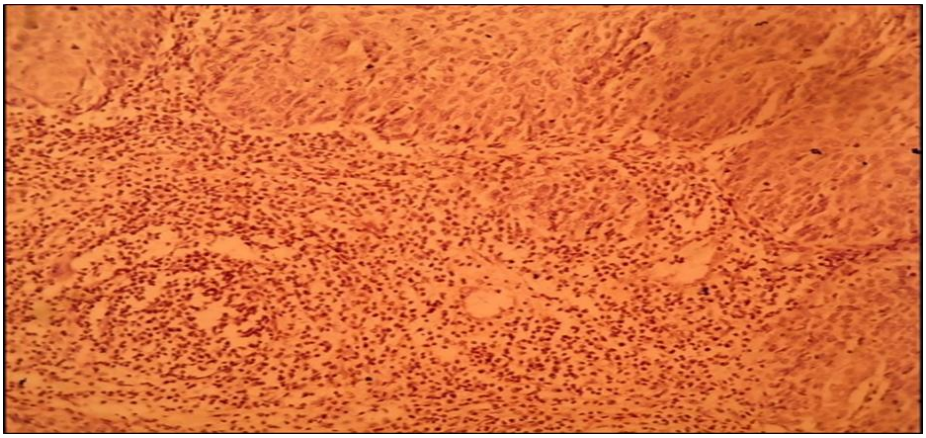

Figure1. IHC CD20. "3+" positive reaction. Lymphoid tissue stained brown. Cervical cancer without recurrence.

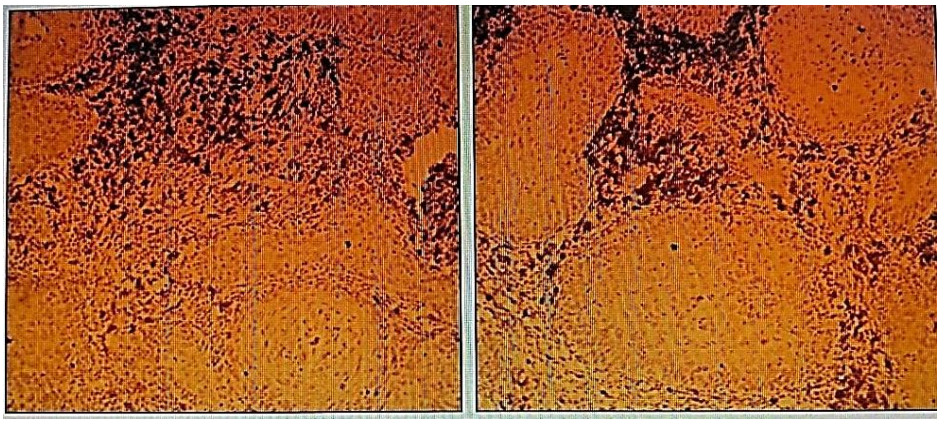

Figure 2. IHC CD 20. "0"-absence of lymphoid infiltrate. Recurrent form

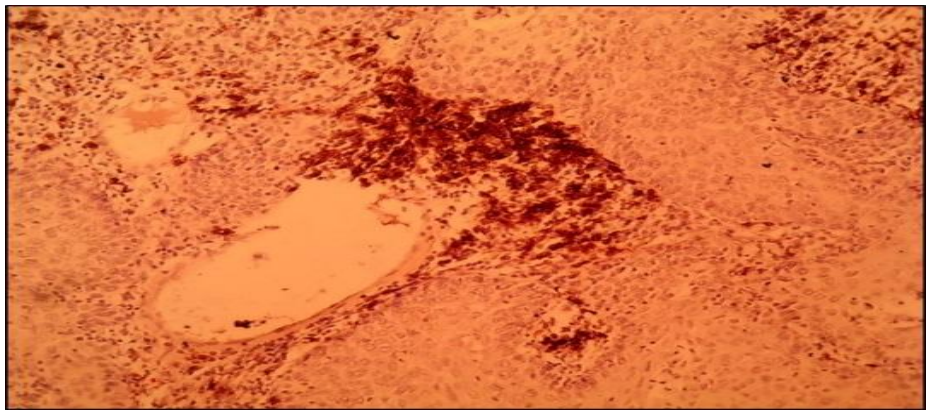

Figure 3 . IHC CD3. "3+" positive reaction. Lymphoid tissue stained brown. Cervical cancer without recurrence.

We found a direct correlation between the number of CD20+ macrophages and the number of CD3+ T cells (S = 0.57; p = 0.0001) or the number of CD20+B cells (S = 0.51; p =

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0.0001), especially between the number of D3+ T-cells and the number of CD20+ B-cells (S = 0.71; p = 0.0001).

Patients with relapsed RHM usually had a low density of immune cells present in biopsy specimens (Table 1); In the group without recurrence of RHM, 30.8% of patients had low CD3+ infiltrate levels and 51.6% had low CD20+ infiltrate levels. Only a limited proportion of patients in the relapse group showed intense infiltrates, 6.4% for CD3+, 3.2% for CD20+. Cases without relapse usually presented with a more intense immune infiltrate. Relapse was associated with a low cellular immune response. All of the above-mentioned correlations were statistically significant at the $p < 0.05$ level. Statistically significant differences between CD3+, CD20+ expression also demonstrated that among relapsed and non-relapsed RSM:

$z1 = -2.98$, $p < 0.002$, for CD3+; $z2 = -2.59$, $p < 0.006$, CD3+ densities of both intra- and peritumoral tissue; in addition, according to the multiple regression model, CD3+ could be considered a powerful prognostic factor for relapse ($F = 10.56$; $p < 0.001$). We identified several differences in immune cell densities and, therefore, in cellular immune response between patients with and without relapsed cervical cancer. Generally, higher immune cell densities occurred in patients without relapse, whereas lower densities in all the two cell subtypes mentioned were associated with relapse. More than half of our relapsed patients presented with low CD3+ T-cells and CD20+ B-cells.

The correlations described between CD3+, CD20+ expression and relapse, even if moderate, are statistically significant at the "p" level less than 0.05. High cell density is associated with RSM survival, whereas relapse is associated with a low cellular immune response.

We demonstrated that CD3+ is a powerful Prognostic factor for recurrence using several Regression models (ANOVA: $F = 10.56$; $p < 0.001$;).

Table 1. Distribution of patients by recurrence and immune response factors.

Option	Cervical Cancer Without Recurrence n=31	Cervical cancer with recurrence n=36
CD3		
Low lymphoid infiltrate	**9 (29 %)**	**18 (50%)**
Intense lymphoid infiltrate	**5 (16,1%)**	**3 (8,3%)**
CD20		
Low lymphoid infiltrate	**11 (35,6%)**	**13(36.1%)**
Intense lymphoid infiltrate	**6 (19.3%)**	**2 (5,5%)**

CONCLUSION

Without recurrence, patients had elevated CD3 and CD20 cell densities, and patients with Relapsed and severe disease had low lymphoid densities. As demonstrated by our

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results, the number of CD3+ T-lymphocytes infiltrating tumor tissue increased survival for both stage IB cervix and stage II B .CD3+ and CD 20 represented an independent survival factor in patients without relapse. Thus, major differences in cellular immune response in cervical cancer patients with and without recurrence have been demonstrated, allowing CD3 and CD20 to be used as potential prognostic biomarkers.

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