Levels of some cellular adhesion molecules (CEA, sICAM-1, sVCAM-1, and E-selecting) in patients affected with colon and urinary bladder cancer during pre and post-operative surgery

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Summary

As inflammatory processes are initiated with a recruited high number of inflammatory cells by intercellular adhesion molecules, also cancerous cells have the same pathways of leukocytes to invade secondary areas. The present study included 60 subjects, healthy and patient men, their ages ranged between 30 to 65 years old. A total number of patients were 30 men and classified into two groups, the first group 15 men affected with invasive colon cancer and the second group complained from bladder carcinoma. The biochemical parameters were conducted before the surgical operation and after the surgical operation (postoperative) the same biochemical parameters were repeated again with the preparation of histological sections. The other number of subjects (30 men) was healthy and served as a control group. Data obtained from this study indicated a significant increase (p<0.001) in the levels of carcinoembryonic antigen (CEA), soluble intercellular adhesion molecules-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), and E-selectin in patients men affected with colon and urinary bladder cancer (preoperative and postoperative) compared to healthy men. Whereas, it had been found that there was a significant drop (p<0.001) in the levels CEA, sICAM-1, sVCAM-1, and E-selectin of both patient groups (pre and postoperative) when compared between them. Concerning histological changes, results showed many histological changes of both colon and urinary bladder. In colonic adenocarcinoma, there was invasive carcinoma with architectural and cytologic features resembling villous adenoma. May had traditional invasive component or invade by pushing. Mucinous features often present, and epithelial islands in desmoplastic stroma is a helpful finding. In regard to urinary bladder carcinoma, there were many traditional changes were presented included Predominantly disorderly appearance (loss of linear orientation perpendicular to basement membrane) at low power with prominent architectural and cytologic abnormalities. Often have complex papillary architecture showing anastomosis of papillae and confluence on low-power examination. Often cellular dyscohesion and denudation. More nuclear pleomorphism / anaplasia than low grade, clumped chromatin, irregular nuclear contour, and prominent nucleoli, irregularly clustered cells with crowding and overlapping, disorganized epithelium, mitotic figures at all levels including surface, which may be atypical. Data obtained from this study is an indication that the levels of intercellular adhesion molecules are significant diagnostic markers in invasive malignant tumors and their levels proportionate directly with presence and tumor mass.

Keywords: Adhesion molecules, tumor, metastasis

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Introduction

The cell adhesion molecules have many cellular functions including growth and, migration, and differentiation, moreover, these biochemical compounds have other essential functions that involve cell-cell interaction and make the cells to interact or bind with components of intercellular ground substances \[1\]. Previously, the adhesion molecules such as ICAM-1, VCAM-1, E–selectin and P–selectin were intensely studied in the inflammatory process because they have functions for recruiting white blood cells on surfaces of endothelial cells of vasculature system before they cross toward inflamed areas. Cancerous cells have also been found the same pathways conducted by leukocytes to invade the secondary organs. Thus, tumor cells express ligands (adhesion molecules) that facilitate their binding with endothelial cells \[2\]. In cancer, there is dysregulation of cell-cell adhesion and cell-matrix adhesion and their roles in the progression of many begin and malignant tumor \[3\]. Tumor cells have the ability to migrate from their original locations and enter into lymph and blood vasculature (metastasis) and then after reach to invade other secondary tissues of the body \[4\].

It is well observed that there is a poor early diagnosis of colon carcinoma but can be detected at a late stage of progression so that it is poor prognosis \[5\]. Carcinoembryonic antigen (CEA) is oncofetal glycoprotein molecules and has a high molecular weight that resembles part of the immunoglobulin superfamily, this antigen links with the plasma membrane of cells \[6\]. Vascular cell adhesion molecule -1 (VCAM-1) is one of the components of the plasma membrane and it likes trans membrane glycoproteins that who much expressed on membranes of endothelial cells lining blood vessels \[7\]. Endothelial cells can sustain their activities to proliferate and migrate initiating angiogenesis of wounds and tumors, one of the most of adhesion molecules is soluble vascular adhesion molecules -1 (sVCAM-1) which play a key role to make chemotaxis of endothelial cells in order to initiate angiogenesis process \[8\].

Materials and methods:-

Subjects of study

The present study was carried out in Hilla teaching hospital and center of oncology, Marjan medical city – Babylon during the period from August 2018 to May 2019. The total number of subjects was sixty men (60 men) of both patients and healthy subjects and their ages ranged between 30 to 65 years old. Patients (30) were subdivided into two groups, the first group included 15 men affected with invasive colon carcinoma and the second group (15 men) complained from invasive urinary bladder carcinoma. All clinical, X-ray, sonar, endoscopy and specific laboratory investigations were performed to patients for diagnosis of cancer. Before surgical operations (preoperative), blood samples were collected from both groups of patients and sera were obtained from blood samples to perform selected and targeted biochemical parameters of the present study. After surgical operations (postoperative), histological sections of removed tissues were performed and after...
period elapsed (one month) when patients administered doses of chemotherapy, also blood samples were collected again in order to estimate the same biochemical parameters that carried out before surgical operations. Concerning healthy men (30 men) were free from chronic diseases and diagnosed by a consultant physician and used as a control group and the same biochemical investigations had been repeated again.

**Methods**

**Biochemical parameters:**
Determination of carcinoembryonic antigen, soluble vascular adhesion molecule –1, soluble intercellular adhesion molecule -1, and E- selectin were determined by the ELISA technique according to instructions of Elabscience Company.

**Histological sections**
Histological sections were prepared according to the procedure conducted by [9] and stained with eosin hematoxylin stain [10].

**Statistical analysis**
Results of the present study were expressed means ± standard error (SE). Student t-test was used to explain differences among studied groups by using computer program SPSS version 16. The lowest significant limit among tested groups was p < 0.05 [11].

**Results**
Data of the present study which are showed in tables 1,2, 3,4,5,6 indicated a significant increase (p <0.05 ) in the levels of CEA, sICAM -1, sVCAM -1, and E- selectin in all patient men affected with colon and urinary bladder cancer when compared with their counterparts of healthy men. Also, these parameters remain significantly elevated in postoperative patients in comparison with healthy subjects. On the other hand, their levels tend to be significantly decreased (p<0.05) in postoperative patients compared to preoperative patients.

**Table (1):** Means of CEA, sICAM-1, sVCAM-1 and sE –selectin in male patients affected with colon cancer (preoperative) and healthy subjects.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Healthy</th>
<th>Preoperative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA (ng/ml)</td>
<td>1.73±0.09</td>
<td>14.12±0.61</td>
<td>0.00041</td>
</tr>
<tr>
<td>sICAM -1 (ng/ml)</td>
<td>123.15±4.36</td>
<td>793.89±26.67</td>
<td>0.00013</td>
</tr>
<tr>
<td>sVCAM -1 (ng/ml)</td>
<td>152.11±3.03</td>
<td>1182.2±96.85</td>
<td>0.00025</td>
</tr>
<tr>
<td>sE- Selectin (ng/ml)</td>
<td>16.94±1.35</td>
<td>95.97±2.91</td>
<td>0.00015</td>
</tr>
</tbody>
</table>

-Values are means ± SE.
- Values are significantly different at p<0.05.
Table (2): Means of CEA, sICAM-1, sVICAM-1 and sE-selectin in male patients affected with colon cancer (postoperative) and healthy subjects.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Healthy</th>
<th>Postoperative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA (ng/ml)</td>
<td>1.73±0.09</td>
<td>8.02±0.39</td>
<td>0.00017</td>
</tr>
<tr>
<td>sICAM-1 (ng/ml)</td>
<td>123.15±4.36</td>
<td>457.31±18.05</td>
<td>0.00064</td>
</tr>
<tr>
<td>sVICAM-1 (ng/ml)</td>
<td>152.11±3.03</td>
<td>748.30±28.67</td>
<td>0.00016</td>
</tr>
<tr>
<td>sE-Selectin (ng/ml)</td>
<td>16.94±1.35</td>
<td>52.10±3.19</td>
<td>0.00072</td>
</tr>
</tbody>
</table>

-Values are means ±SE
-Values are significantly different at p <0.05.

Table (3): Means of CEA, sICAM-1, sVICAM-1 and sE-selectin in male patients affected with colon cancer (preoperative and postoperative) and healthy subjects.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA (ng/ml)</td>
<td>14.12±0.61</td>
<td>8.02±0.39</td>
<td>0.00007</td>
</tr>
<tr>
<td>sICAM-1 (ng/ml)</td>
<td>793.89±26.67</td>
<td>457.31±18.05</td>
<td>0.00012</td>
</tr>
<tr>
<td>sVICAM-1 (ng/ml)</td>
<td>1182.2±96.85</td>
<td>748.30±28.67</td>
<td>0.001</td>
</tr>
<tr>
<td>sE-Selectin (ng/ml)</td>
<td>95.97±2.91</td>
<td>52.10±3.19</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

-Values are means ±SE
-Values are significantly different at p <0.05.

Table (4): means of CEA, sICAM-1, sVICAM-1 and sE-selectin in male patients affected with bladder cancer (preoperative) and healthy subjects.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Healthy</th>
<th>Preoperative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA (ng/ml)</td>
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<td>8.37±0.37</td>
<td>0.00021</td>
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<tr>
<td>sICAM-1 (ng/ml)</td>
<td>123.15±4.36</td>
<td>684.91±21.59</td>
<td>0.00064</td>
</tr>
<tr>
<td>sVICAM-1 (ng/ml)</td>
<td>152.11±3.03</td>
<td>965.26±50.23</td>
<td>0.0001</td>
</tr>
<tr>
<td>sE-Selectin (ng/ml)</td>
<td>16.94±1.35</td>
<td>79.20±3.36</td>
<td>0.00020</td>
</tr>
</tbody>
</table>

-Results are means ±SE
-Results are significantly different at p <0.05.
Table (5): means of CEA, sICAM-1, sVICAM-1 and E–selectin in male patients affected with bladder cancer (postoperative) and healthy subjects.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Healthy</th>
<th>postoperative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA (ng /ml)</td>
<td>1.73±0.09</td>
<td>6.11±0.31</td>
<td>0.0009</td>
</tr>
<tr>
<td>sICAM -1 (ng/ ml)</td>
<td>123.15±4.36</td>
<td>410.33±22.22</td>
<td>0.0003</td>
</tr>
<tr>
<td>sVICAM - 1 (ng /ml)</td>
<td>152.11±3.03</td>
<td>446.23±22.70</td>
<td>0.0003</td>
</tr>
<tr>
<td>s E- Selectin (ng /ml)</td>
<td>16.94±1.35</td>
<td>50.17±2.29</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

-Results are means ±SE.

-Results are significantly different at p<0.05.

Table (6): means of CEA, sICAM-1, sVICAM-1 and E–selectin in male patients affected with bladder cancer (preoperative and postoperative) and healthy subjects.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>preoperative</th>
<th>Postoperative</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA (ng /ml)</td>
<td>8.37±0.37</td>
<td>6.11±0.31</td>
<td>0.001</td>
</tr>
<tr>
<td>sICAM -1 (ng/ ml)</td>
<td>684.91±21.59</td>
<td>410.33±22.22</td>
<td>0.00071</td>
</tr>
<tr>
<td>sVICAM - 1 (ng /ml)</td>
<td>965.26±50.23</td>
<td>446.23±22.70</td>
<td>0.00047</td>
</tr>
<tr>
<td>s E- Selectin (ng /ml)</td>
<td>79.20±3.36</td>
<td>50.17±2.29</td>
<td>0.000076</td>
</tr>
</tbody>
</table>

-Results are means ± SE

-Results are significantly different at p<0.05.

Figure (1): Shows transitional cell carcinoma of urinary bladder: Aggregates of transitional cells arranged in sheets and forming papillary structures invading the smooth muscle fibers. H&E. X100.
Transitional Cell Carcinoma
Predominantly disorderly appearance (loss of linear orientation perpendicular to basement membrane) at low power with prominent architectural and cytologic abnormalities. Often have complex papillary architecture showing anastomosis of papillae and confluence on low-power examination. Often cellular dyscohesion and denudation. More nuclear pleomorphism, anaplasia than a low grade, clumped chromatin, irregular nuclear contour, and prominent nucleoli, irregularly clustered cells with crowding and overlapping, disorganized epithelium, mitotic figures at all levels including surface, which may be atypical. Some tumors may show more monomorphic nuclei; nuclear rounding is common. Highest grade tumors may not appear urothelial, may have indistinct cell borders. Associated with carcinoma in situ or dysplasia in the adjacent nonpapillaryurothelium. Grade according to highest grade within a tumor, ignoring minuscule areas of the higher-grade tumor. The high-grade designation is the clinical threshold for adjuvant intravesical therapy.

Figure (2): Colonic adenocarcinoma with irregular glands invading the upper lamina propria. H&E. X100.

Colon carcinoma
Invasive carcinoma with architectural and cytological features resembling villous adenoma. May have a traditional invasive component or invade by pushing. Mucinous features often present. Epithelial islands in desmoplasticstroma is a helpful finding.

Discussion
Most, if not all, several previous studies and measurements of many serum biochemical markers were conducted to provide indicators for the incidence. Prognosis of several tumors, of these biochemical markers, are CEA and tissue polypeptide antigens \(^{[12]}\). The present study was investigated available cellular adhesion molecules which perhaps a vital role to facilitate metastasis of cancerous cells to invade other secondary organs.
The previous study was consistent with present data and showed that although CEA is a special marker for colorectal and pancreatic cancer it is well-documented to increase its levels of invasive bladder cancer when the tumor invades urothelial layer and these levels tend to drop after chemotherapy and radiotherapy [13, 14]. The previous study of Park [15] confirmed that preoperative of CEA, histological changes of cancerous tissues and site of the tumor can give an indicator for fate and outcome of patients. High levels of CEA during the preoperative period can indicate poor prognosis of patients affected with colon cancer and this report documented there is no relation with age, tumor location and Dukes stage [16].

The previous investigation indicated that there are many diseases cause increase of carcinoembryonic antigens such as inflammatory condition including pancreatitis, obstructive pulmonary diseases, and enteritis as well as it is also increased with old ages, it is well documented that progression of colon cancer is associated increase levels of CEA and tend to be decreased after surgical operation [17].

During stage II and III of colorectal carcinoma, it has been found that CEA levels are unregulated of patients complained of colorectal carcinoma 18. Both intercellular adhesion molecule – 1 and vascular adhesion molecule -1 are groups from immunoglobulin families that enhance the invasion of cancer cells [19]. Increase expression of ICAM-1 is related to progression and aggressive of tumor pattern [20]. However, there is evidence indicated a drop in cell adhesion molecule -1 in several cancer tissues of human organs [21].

In addition, the lack of expression of cell adhesion molecule -1 has been related to the progression of cancer cells and also related to non-invasive bladder cancer and different stages of bladder cancer [22]. Another in vitro study carried out by Campbell [23] proved the role of ICAM-1 and its relation with leukocyte function antigen -1 act to have an interaction between bladder cancerous cells and cytokine called lymphokine-activated killer cells and then concluded that ICAM-1 can play an effector factor for induction immune responses to urinary bladder cancer. In fact, cell adhesion molecules -1 exerts their functions to regulate and control cell to cell interaction and adhesion, the alteration of their expression was found associated with tumor development and progression, the authors demonstrated that levels of cell adhesion molecule -1 protein were decreased significantly in bladder cancer tissues in a comparison with healthy mucosa. Also, this study concluded that overexpression of ICAM -1 protein can inhibit cancer cells and their proliferation and invasion by apoptosis [24]. According to pathological point view, the malignant cells act to ensure their penetration across tissues, they exert their effects to destroy and damage of intercellular adhesion molecule through desquamation of cells that constitute lamina property and by this process the malignant cells become free and motile to invade several tissues and development metastasis [25].

In regard to the proliferative mechanism of tissues, it is obvious that to sustain oxygen and nutrition demands of tumor mass that having volume ranged between 1 -2 mm3, they require the proliferation of new blood vessels [26]. Another study appears consistent with the present study and explained that levels of VCAM-1 remain
elevated dominantly during the first month of the post-operative period to stimulate the neovascularization process and growth of tumor cells that residual after surgery. Moreover, VCAM-1 stimulates and increase enlargement and distention or metastasis of many solid tumors, it is found that scam-1 concentrations were significantly increased in patients with colon cancer compared to healthy subjects and this biochemical parameter considers the marker for progression of cancer during preoperative stage [27].

Another observational study showed overexpression of intercellular adhesion molecules such as sVCAM-1, ICAM-1 and E-selectin after vascular endothelial growth factor to stimulate endothelial cell proliferation and explained that these adhesion molecules were correlated significantly with each other [28, 29]. It is well documented that there is a primary step in tumor metastasis involves adhesion of tumor cells to endothelium, the intercellular adhesion molecules that are mostly presented by endothelium might be implicated in interaction with bladder tumor cells [30]. Previous data hypothesized that endothelial cells act to decrease of carcinoembryonic antigen – cell adhesion molecules to activate vascularization across overexpression of both vascular growth factors including VEGF- C and VEGF –D, however, their observations become inverse with endothelial cells that express up-regulation of CEA – ICAM -1 to increase angiogenesis [31].

It observed there is a conspiracy between present data and previous study that revealed increasing levels of P-selectin, E – selectin, sVCAM-1 and ICAM-1 in patients suffering from bladder carcinoma compared to healthy subjects [32]. In fact, selectin mediates the first interaction and attachment of circulating tumor cells with endothelial cells. The local production of chemokines located on apical surfaces of endothelial cells makes the tumor cells to enhance their adhesion with a member of IG – CAM especially ICAM and facilitating the migration of cancer cells across blood vessels (Extravasation) [33]. The previous studies demonstrated increasing levels of adhesion molecules including E – selectin, sVCAM, and ICAM and this study found that these molecules are significantly associated with stages of cancer and metastasis. Furthermore, it explained that these parameters tend to decrease after a surgical operation such as colon resection, so that, these data concluded the adhesion molecules give an indicator of the progression of cancer and metastasis [34].

There is a relevance of VCAM to increase angiogenesis, since, there is evidence indicates increase VCAM in tissues rich with new vasculature (angiogenesis) and these levels become dropped in tissues without microvessels in gastric vessels [35]. The present results agree with the study of Sato [36] who confirmed an interaction between CA 19 – 9 and E –selectin in propagation metastasis of colon cancer. Also, present data are consistent with previous studies that showed an increase of E- selecting, sVCAM-1 and sCAM-1 of patients with bladder cancer having muscle-invasive tumor [37].

In conclusion, data mentioned and illustrated above can be given a remarkable indicator indicates that the levels of intercellular adhesion molecules remain at a high level although surgical operation and chemotherapy so that these molecules may be confirmed remaining tumor cells invade the other tissues of the body.
References


