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Cancer Antigen 125 Levels in Inflammatory Bowel Diseases

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Background: Cancer antigen 125 (CA-125) is a tumor marker used for the diagnosis and monitoring of ovarian carcinoma. It can also be elevated in endometriosis, inflammations, and in nongynecological malignancies. Up to date, serum CA-125 levels in inflammatory bowel diseases (IBD) have not been studied before. Aim: To assess the levels of CA-125 in patients with ulcerative colitis (UC) and Crohn's disease (CD). Methods: Serum levels of CA-125 were investigated in 68 cases with UC (male/female: 47/21), 32 CD (male/female: 21/11), and 31 healthy controls (male/female: 16/15). Levels of CA-125 were also compared among UC patients according to lesion location, severity, and activity of CD. Results: Serum CA-125 levels were 17.29 ± 24.50 U/ml, 15.56 ± 20.74 U/ml, and 8.85 ± 2.62 U/ml in patients with UC, CD, and healthy controls, respectively. Serum CA-125 levels were significantly higher in UC compared to control group ($P = 0.001$). Serum CA-125 levels were higher in CD patients compared to control group but there was no significance ($P = 0.087$). Serum CA-125 levels were higher in pancolitis compared to distal type and left-sided UC. Conclusions: Our data suggest that serum CA-125 levels may be increased in patients with IBDs. J. Clin. Lab. Anal. 23:244–248, 2009.

Key words: cancer antigen 125; ulcerative colitis; Crohn's disease

INTRODUCTION

Inflammatory bowel disease (IBD) embodies a spectrum of disorders that affect the gastrointestinal tract, the two major entities being Crohn's disease (CD) and ulcerative colitis (UC). IBD is characterized by chronic inflammation of the intestine with periods of exacerbations and remissions (1,2). To accurately monitor intestinal inflammation, symptoms and clinical examinations, combined in clinical indices, on the one hand, and endoscopy with histology, additional radiological, or cross-sectional imaging techniques, on the other hand, are required (3–5).

Many noninvasive tests have been studied for diagnosis and determining the activation degree of IBD (including, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), P-ANCAs and ASCAs). However, an ideal test has not been found yet (6–8).

CA-125 is a valuable marker for diagnosis and monitoring of ovarian carcinoma (9,10). It is known that CA-125 may be elevated in other malignancies and inflammatory events in abdomen (11). For all that hitherto there is no study reported examining the relation between IBD and CA-125. The aim of this study was to assess the levels of CA-125 in patients with IBD.

MATERIALS AND METHODS

A total of 68 UC patients (male/female: 47/21) and 32 CD patients (male/female: 21/11) were collected. A total of 31 healthy individuals (male/female: 16/15) were used as controls. Diagnosis of UC and CD was based

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on standard clinical, radiological, endoscopic, and histological criteria. Written informed consent was obtained from all the participants in the study.

The clinicians involved in patient care and gastroenterologists who performed colonoscopies were not blinded to the patients' diagnosis. However, all laboratory analyses were performed in a blinded fashion.

In patients with UC, clinical activity was defined according to Truelove–Witts criteria (12). In CD, disease activity was determined with the CD activity index of Best et al. (13). Endoscopic activity index was defined according to Rachmilewitz Index in patients with UC (14).

CA-125 levels were determined on an Access Immunoassay Analyzer (Beckman Coulter, Fullerton, CA) with original reagents.

The Statistical Package for Social Sciences (SPSS) 13.0 for windows was used to analyze the data. All data were analyzed in terms of mean $\pm$ standard deviation (SD). For continuous variables, Kruskal–Wallis test and Mann–Whitney *U* test were used to analyze the variance among groups if appropriate. Pearson correlation analysis was used to analyze the data. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values of CA-125 level to identify with maximum sensitivity and specificity the detection of UC. *P* values below 0.05 were considered as statistically significant.

RESULTS

The biochemical tests and demographics of the patient and control population studied are shown in Table 1. The mean age of patients with UC, CD, and healthy controls were 42.89 ± 13.13, 41.40 ± 12.65, and 43.48 ± 18.47 years, respectively. Biochemical tests are summarized in Table 1. Serum CA-125 levels were 17.29 ± 24.50 U/ml, 15.56 ± 20.74 U/ml, 8.85 ± 2.62 U/ml for patients with UC, CD, and control group respectively (Fig. 1). Serum CA-125 levels were significantly different between groups ($P = 0.002$) (Table 2). There was a statistically significant difference in CA-125 levels between UC and control group ($P = 0.001$). Serum CA-125 levels were higher in CD patients compared to control group; however, the difference was nonsignificant ($P = 0.087$). There was no statistically significant difference in CA-125 levels between UC group and CD group ($P = 0.1$).

Serum CA-125 level was not correlated with the severity of UC ($P = 0.887$) (Table 3). There was no statistically significant difference in CA-125 levels between groups according to lesion location ($P = 0.837$) (Table 3). However, serum CA-125 levels were higher

TABLE 1. Biochemical Tests and Demography of the Patients and Controls

	Ulcerative colitis ($n = 68$)	Crohn's disease ($n = 32$)	Control ($n = 31$)
Sex			
Female	21 (30.9%)	11 (34.4%)	15 (48.4%)
Male	47 (69.1%)	21 (65.6%)	16 (51.6%)
Age	42.89 ± 13.13	41.40 ± 12.65	43.48 ± 18.47
Localization			
Distal	21 (34.4%)		
Left-sided	18 (29.5%)		
Pancolitis	22 (36.1%)		
Colonic		7 (25.9%)	
Ileocolonic		19 (70.4%)	
Ileal		1 (3.7%)	
Activation			
Mild	45 (68.2%)		
Moderate	11 (16.7%)		
Severe	10 (15.2%)		
150 > CDAI		21 (65.6%)	
150 < CDAI		11 (34.4%)	
Operated	1 (%)	4 (13.8%)	
Hemoglobin	13.22 ± 2.11	12.64 ± 1.82	
Platelet	203.49 ± 101.07	381.40 ± 123.04	
WBC	8.14 ± 2.67	8.06 ± 4.38	
CRP	8.22 ± 9.09	29.16 ± 59.29	
ESR	25.16 ± 25.11	41.56 ± 23.05	
Fibrinogen	3.76 ± 1.49	4.75 ± 1.66	
Albumin	4.19 ± 0.54	4.42 ± 1.87	

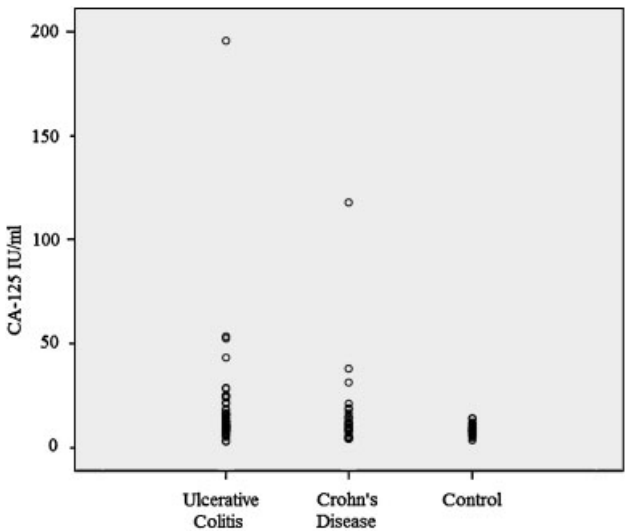

Fig. 1. CA-125 levels in UC, CD, and control groups.

TABLE 2. Comparison of CA-125 Levels Between Groups

	CA-125 (U/ml)	*P*
Ulcerative colitis ($n = 68$)	17.29 ± 24.50	
Crohn's disease ($n = 32$)	15.56 ± 20.74	0.002
Control ($n = 31$)	8.85 ± 2.62	
Ulcerative colitis–Control		0.001
Ulcerative colitis–Crohn's disease		0.1
Crohn's disease–Control		0.087

TABLE 3. CA-125 Levels According to Localization and Activation Degree in Ulcerative Colitis

	CA-125 (U/ml)	*P*
Localization		
Distal type ($n = 20$)	13.38 ± 8.23	0.837
Left type ($n = 18$)	15.23 ± 11.94	
Pancolitis ($n = 22$)	24.21 ± 39.80	
Degree of activation		
Mild ($n = 45$)	18.81 ± 29.27	0.887
Moderate ($n = 11$)	16.27 ± 13.11	
Severe ($n = 10$)	12.24 ± 6.14	

in pancolitis compared to distal and left-sided UC. The patients with active CD had a higher serum CA-125 levels compared to patients with inactive CD but the difference was nonsignificant ($P = 0.322$) (24.28 ± 32.72 U/ml vs. 10.52 ± 5.02 U/ml).

ROC curve analysis suggested that the optimum CA-125 level cut-off points for UC was 9.2 U/ml, with a sensitivity and specificity of 74 and 62%, respectively (AUC = 0.733).

DISCUSSION

In this study we demonstrated that serum CA-125 levels increase in UC. Additionally, although statistically nonsignificant, serum CA-125 levels were higher in CD patients compared to control group. Serum CA125 levels were higher in pancolitis than left-sided and distal type UC.

IBDs comprise two distinct entities, UC and CD. IBD is characterized by a chronic course in which phases of remission of variable length are interrupted by acute episodes (1). The presence of active gut inflammation in patients with IBD is associated with an acute phase reaction. In serum, the white blood cell count, platelet count, or ESR can change during inflammatory states, but these measures are hampered by a low sensitivity and specificity for intestinal inflammation, and do not adequately reflect disease activity (2). CRP has been found to be associated with clinical, endoscopic, and radiologic activity in IBD (7).

Several antibodies have been described in IBD, the two most intensively studied antibodies are P-ANCAs and ASCAs. They are markers for UC and CD, respectively. Their role as diagnostic serologic markers for IBD appears to be limited because of their lower sensitivities (15,16). Stool tests have also been studied to detect an ideal marker. Lactoferrin, calprotection, and polymorphonuclear neutrophil-elastase are fecal markers that may reflect intestinal inflammation in IBD. The sensitivity, specificity, and diagnostic accuracy of fecal markers with reference to clinical disease indices and endoscopically measured inflammation remain unclear (17–20). In a recent study it was shown that lactoferrin, calprotein, and PMN-elastase are superior to CRP, and none of them is superior in the ability to reflect endoscopic inflammation (21). In another new study it was shown that fecal myeloperoxidase, eosinophil protein X and IL-1 β have a high sensitivity in conforming active UC and a high efficiency in detecting changes in disease activity. However, they are new and expensive markers (22).

The glycoprotein CA-125, and a cell surface antigen recognized by the OC-125 murine monoclonal antibody, has become widely used clinically in gynecologic oncology. Bast et al. first introduced its use as a marker for ovarian cancer in 1983 (23). It has been extensively studied in the diagnosis and monitoring of epithelial ovarian carcinoma. CA-125 is expressed in coelomic epithelium during fetal development. This epithelium lines body cavities. The known distribution of CA-125 is in mesothelial cells of the peritoneum, pleura, and pericardium, in the epithelium of the fallopian tubes, endometrium, and endocervix. Elevated serum CA-125 levels have been reported in the literature in multiple

benign and malignant pathologies with serosal involvement (cirrhosis, tuberculous, peritonitis, pancreatic cancer, heart failure, etc.) (11,24).

Several mechanisms have been suggested to explain serum CA-125 level increment. First, malignant tissue itself produces CA-125 (9,10). Second, tumoral invasion to serosa may induce mezothelial cells to synthesize CA-125. Also, collected fluid during the course of benign or malignant inflammation may induce CA-125 production by mezothelial cells (9,24–26). On the other hand, cases with heart failure without effusion may have increased serum CA-125 levels. Induction of mesothelial cells via cytokines has been accused as a possible mechanism in those patients (27).

We determined increased levels of CA-125 in patients with IBD. However, the level was significant in only UC group. Interestingly, elevations of CA-125 in IBD were not related to disease severity. In cases with uncomplicated UC there is no apparent mechanism to induce serosa directly or indirectly. Therefore, there is no known mechanism to explain the increased CA-125 levels in UC patients. However, immunologic mechanisms have role on pathogenesis. CD is usually described as a prototypical T-helper (Th) 1 disease because the primary mediators of inflammation are the Th1 cytokines interleukin-12 (lL-12), interferon-γ, and tumor necrosis factor. However, UC is often viewed as a Th2-type condition because of reports of increased mucosal expression of the Th2 cytokine IL-4, IL-5, IL-10, and IL 13 (28–30). As a summary, there is a cytokine activation in patients with IBD. Those cytokines may have a role in the elevation of serum CA-125 levels as it is in cases with heart failure without effusion. In a study it has been reported that, UC cases had more prominent cytokine secretion in comparison to CD patients (31). That may explain the higher CA-125 levels in those patients with UC. Moreover, as a consequence of increased inflamed surface, UC cases with pancolitis have higher CA-125 levels. However, as a limitation of this study, we cannot explain which cytokines are involved and induce the target mechanisms.

In conclusion, CA-125 may be increased in patients with IBD, particularly in UC. Among the causes of elevated serum CA-125 levels, IBD should be kept in mind in the differential diagnosis.

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