

• CLINICAL RESEARCH •

Effects of depression on parameters of cell-mediated immunity in patients with digestive tract cancers

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CONCLUSION: Depression occurs with a high incidence in patients with cancers of the digestive tract, which probably is not the sole factor leading to the impairment of immunological functions in these cases. However, comprehensive measures including psychological support should be taken in order to improve the immunological function, quality of life and clinical prognosis of these patients.

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Abstract

AIM: To evaluate the effects of depression on parameters of cell-mediated immunity in patients with cancers of the digestive tract.

METHODS: One hundred and eight adult patients of both sexes with cancers of the digestive tract admitted between March 2001 and February 2002 in the Department of Medical Oncology, First Affiliated Hospital of Xi'an Jiaotong University were randomly enrolled in the study. The Zung self-rating depression scale (SDS), Zung self-rating anxiety scale (SAS), numeric rating scale (NRS) and social support rating scale (SSRS) were employed to evaluate the degree of depression and their contributing factors. In terms of their SDS index scores, the patients were categorized into depression group ($SDS \geq 50$) and non-depression group ($SDS < 50$). Immunological parameters such as T-lymphocyte subsets and natural killer (NK) cell activities in peripheral blood were determined and compared between the two groups of patients.

RESULTS: The SDS index was from 33.8 to 66.2 in the 108 cases, 50% of these patients had a SDS index more than 50. Similarly, the SAS index of all the patients ranged from 35.0 to 62.0 and 46.3% of the cases had a SAS index above 50. Cubic curve estimation showed that the depression was positively correlated with anxiety and negatively with social support. Furthermore, the depression correlated with the tumor type, which manifested in a descending order as stomach, gallbladder, pancreas, intestine, esophagus, duodenum and rectum, according to their correlativity. Step-wise regression analysis suggested that hyposexuality, dispiritment, agitation, palpitation, low CD_{56} and anxiety were the significant factors contributing to depression. More severe anxiety (49.7 ± 7.5 vs 45.3 ± 6.9 , $P < 0.05$), pain (6.5 ± 2.8 vs 4.6 ± 3.2 , $P < 0.05$), poor social support (6.8 ± 2.0 vs 7.6 ± 2.1 , $P < 0.05$), as well as decline of lymphocyte count (0.33 ± 0.09 vs 0.39 ± 0.07 , $P < 0.05$) and CD_{56} (0.26 ± 0.11 vs 0.29 ± 0.11 , $P < 0.05$) were noted in the depression group compared with those of the non-depression patients. However, fewer obvious changes in CD_4/CD_8 ratio and other immunological parameters were found between the two groups.

INTRODUCTION

Cancers of the digestive tract continue to be one of the most common malignancies in human worldwide^[1-14], in which gastric, esophageal, colorectal and liver cancers are among the top ten malignant tumors in China and account for 63% of total cancer mortality^[11]. Depressive symptoms such as pervasive senses of hopeless, helpless, valueless, despair, guilty, punishment and self-deprecatory thinking are often found in cancer patients. When severely enough, it may cause negative effects on the antitumor therapy, immunological function, prognosis, as well as the quality of life^[15,16]. However, up to the present, much attention has been paid to the effects of depression on patients with several kinds of malignancies^[17-20] except that of the digestive tract. Besides, despite mounting evidence that psychiatric depression heightens risk for cancerous morbidity and mortality, little is known about the detailed mechanisms responsible for this association, which is no doubt of importance in the improvement of therapy for cancer patients.

In the present study, we therefore investigated the effects of depression on cell-mediated immunity and its contributing factors in 108 patients with cancers of the digestive tract by SDS^[21] and other questionnaires, as well as immunological parameters including T-lymphocyte subsets and natural killer (NK) cell activities in peripheral blood, in an attempt to provide evidence for the necessities of psychological therapy of these cancer patients.

MATERIALS AND METHODS

Patients

One hundred and eight adult patients of both sexes with cancers of the digestive tract including 24 esophageal, 36 gastric, 4 duodenal, 4 gallbladder, 4 pancreatic, 28 colonic and 8 rectal cancer cases admitted between March 2001 and February 2002 in the Department of Medical Oncology, First Affiliated Hospital of Xi'an Jiaotong University were randomly enrolled in the study. The medical records of these patients were reviewed by investigators and their characteristics such as the family history of cancer and main symptoms were abstracted. Subjects with a history of abnormal mentality or cognitive disorders were excluded from the investigation. All the cancer cases were finally verified by histopathological examinations

and clinically diagnosed as stage I in 14, stage II in 34, stage III in 28 and stage IV in 32 according to TNM classification and the Union International Center of Cancer (UICC) system. The average disease course of the patients was 14 ± 11 months and the average age was 58 ± 9 years with the education background of 7 being graduated from primary school, 25 from junior high school and 76 from senior high school or above. Their performance status (PS) was defined by Eastern Cooperative Oncology Group (ECOG) and social information such as marital and employment status was obtained through an interview. The patients were categorized into depression group and non-depression group in terms of their SDS index scores. The study protocol was in accordance with the guideline for clinical research and approved by the Ethical and Research Committee of the hospital.

Psychological measurements

Zung self-rating depression scale (SDS) The Zung SDS system harbors 20 items of self-evaluation measurements for depressive symptoms^[21]. In the study, the patients were asked to rate each of the items regarding how they felt during the preceding week by a 4-point Likert scale with the 4 representing the most unfavorable response. After the scores of 10 reversely-graded items were adjusted in line with that of the sequentially-scored items, a raw score that was turned out from the total value of 20 items was further converted into a depression-judging variable termed as SDS index, based on which the cases were categorized into 2 levels of psychological conditions. Level 1, SDS index below 50, was considered not significant psychopathologically. Level 2, SDS index equal to or above 50, was suggested the presence of depression. It was not meant for SDS index to offer a strict diagnostic guideline but rather denote levels of depression in symptomatology that might be of clinical significance. Overall, the SDS index was shown to be relatively valid with a high internal consistency that was exhibited by an alpha coefficient of 0.84^[22].

Zung Self-rating anxiety scale (SAS) Just like Zung SDS system, Zung SAS also has 20 items to be scored with the 4-point Likert scale except that there are 5 reversely-scored items, in which the 4 represents the most unfavorable response^[23]. After the scores of 5 reversely-graded items were adjusted in line with that of the sequentially-scored items, a raw score that was turned out from the total value of 20 items was further converted into an anxiety-judging variable termed as SAS index, based on which the cases were categorized into 2 levels of psychological conditions. Level 1, SAS index below 50, was considered not significant psychopathologically. Level 2, SAS index equal to or above 50, was suggested the presence of anxiety.

Numeric rating scale (NRS) NRS consisting of four questions covering pain, nausea, insomnia and appetite was evaluated by using a 0-10 scale, with 0 meaning without symptoms and 10 indicating the situation being as bad as imagined, which was found to be a simple and valid pain measurement in some disease states^[24]. In this study, the patients were asked to circle the number that best described the symptom at its worst during a one-week period.

Social support rating scale (SSRS) SSRS was employed to evaluate the levels of objective, subjective and total social support, as well as the utility of this support^[25].

Study protocols

Two days before the investigation, each item for the psychological measurements was explained by specialized doctors in order to make the patients understand and complete the questionnaires correctly by themselves in a quiet condition to exclude any possible influence. If it could not be completed by the patients for some reasons as sickness or poor education, family members or

physicians in charge were prescribed to do it instead.

On the experimental day, 3.5 ml of peripheral blood was drawn from each patient and anticoagulated by ethylenediaminetetraacetic acid (EDTA), in which 50 μ l of blood was quantified with the Sysmes KX-21 blood counter (Japan) for the measurement of white blood cells, erythrocytes, thrombocytes, and fractions of lymphocytes, granulocytes and monocytes. The other 3.0 ml of blood sample was used to determine natural killer cells (CD₅₆) and T lymphocyte subsets with the EPICS ELITE flow cytometer (American) by individuals blinded to the clinical data of the patients in our immunology laboratory.

Statistical analysis

Experimental data were expressed as $\bar{x} \pm s$. Comparisons between experimental groups were performed by *t*-test to examine the variables with normal distribution and by Mann-Whitney *U* test to assess the other kinds of numerical values. Demographic variables were analyzed by descriptive statistics to evaluate the clinical and sociodemographic characteristics of the studied samples. Curve estimation, stepwise multiple or univariate linear regression and Pearson correlations were adopted to assess the correlation of depression with its possible contributing factors. A *P* value less than 0.05 was considered statistically significant. All statistical procedures were performed with statistical package of SPSS for social science (2000).

RESULTS

Incidence of depression in cancer patients

Questionnaires answered by the enrolled patients were correctly filled in according to the experimental protocol. The scores of SDS 4 grade evaluation are listed in Table 1. In the present study, SDS index was approximately a normal distribution in the 108 cases, ranging from 33.8 to 66.2 and averaging at 50.4 ± 8.8 . Fifty percent of the patients had a SDS index score more than 50. Similarly, SAS index of all the patients ranged from 35.0 to 62.0 and averaged at 46.9 ± 7.7 , 46.3% of the cases had a SAS index score above 50, 29.6% of the enrolled patients had scores above 50 simultaneously for both SDS and SAS indexes. The social support score was between 28 and 56 and averaged at 43.8 ± 7.2 . Curve estimation showed that the depression was positively correlated with anxiety and negatively with social support. Furthermore, the depression correlated with the tumor type, which manifested in a descending order as stomach, gallbladder, pancreas, intestine, esophagus, duodenum and rectum, according to their correlativity.

Factors contributing to depression

Many factors were associated with depression such as cancer pain, anxiety, poor economic status, tumor type, anorexia (X5: I eat as much as I used to), hyposexuality (X6: I enjoy looking at, talking to and being with attractive men/women), dispiritment (X1: I feel downhearted, blue and sad), agitation (X13: I am restless and can not keep still), palpitation (X9: My heart beats faster than usual), fatigue without apparent reasons (X10: I get tired for no reason), CD₅₆₊, *etc.* However, step-wise regression analysis suggested that hyposexuality, dispiritment, agitation, palpitation, CD₅₆ and anxiety were the significant factors contributing to depression (Table 2).

Effects of depression on cell-mediated immunity

More severe anxiety and poor social support were noted in the depression group compared with those of the non-depression patients. As for the parameter changes of cell-mediated immunity in peripheral blood, an increase of granulocyte count and a decline in T-lymphocyte subsets (CD₃, CD₄ and CD₈), erythrocyte and monocyte counts were observed in depression cases, but did not reach a significant level. Lymphocyte count

Table 1 SDS 4 grading of depressive manifestations in patients with gut cancers

Item	Factors	$\bar{X} \pm s$	Grade			
			1	2	3	4
X1	I feel downhearted, blue and sad	1.9±0.8	34	50	18	6
X2	Morning is when I feel best	2.6±1.1	18	42	18	30
X3	I have crying spells or feel like it	1.5±0.9	75	14	14	5
X4	I have trouble sleeping through the night	2.1±1.0	42	22	34	10
X5	I eat as much as I used to	2.6±1.0	22	22	46	18
X6	I enjoy looking at, talking to, and being with attractive men/women	2.6±1.1	25	26	26	31
X7	I notice that I am losing weight	2.4±1.0	18	46	22	22
X8	I have trouble with constipation	2.2±1.1	38	30	22	18
X9	My heart beats faster than usual	1.3±0.6	76	16	8	8
X10	I get tired for no reason	2.3±1.1	34	30	22	22
X11	My mind is as clear as it used to be	1.8±0.9	50	30	22	6
X12	I find it easy to do the things I used to do	2.3±0.9	22	42	30	14
X13	I am restless and can't keep still	1.6±0.9	62	22	18	6
X14	I feel hopeful about the future	2.2±0.9	30	30	42	6
X15	I am more irritable than usual	1.7±1.0	58	26	14	10
X16	I find it easy to make decisions	2.3±1.1	34	26	26	22
X17	I feel that I am useful and needed	1.9±1.0	42	42	10	14
X18	My life is pretty full	1.8±0.8	38	50	14	6
X19	I feel that others would be better off if I were dead	1.4±0.7	70	30	2	6
X20	I still enjoy the things I used to do	2.2±1.0	30	42	18	18

Table 2 Multivariate analysis of contributing factors of depression with step-wise regression

Variable	Unstandardized coefficients (B)	Standardized coefficients (β)	t	P value	Pearson correlation
X1 ^a	4.47	0.36	19 193 329	0.00	0.64
X6 ^a	4.13	0.51	19 076 980	0.00	-0.80
X9 ^a	0.97	0.07	3 266 595.5	0.00	0.65
X13 ^a	1.78	0.15	4 232 747.7	0.00	0.08
Anxiety ^a	6.04E-02	0.06	3 691 620.2	0.00	0.32
CD ₅₆ ^a	-2.33	-0.10	-28 074 903	0.00	-0.18

^aP<0.05 vs nondepression group.

and CD₅₆ were significantly decreased in the depression group compared with those of the non-depression patients ($P<0.05$) as shown in Table 3. However, fewer changes in CD₄/CD₈ ratio and other immunological parameters were found between the two groups.

Table 3 Multiple factors between depression and nondepression groups ($\bar{X} \pm s$)

Parameters	Depressive state	Non-depressive state	P
Anxiety	49.7±7.5 ^b	45.3±6.9	0.003
Pain	6.5±2.8 ^a	4.6±3.2	0.025
Social support	44.0±6.8	44.6±7.7	0.670
Objective support	11.9±3.0	12.5±3.0	0.360
Subjective support	24.8±3.8	24.5±4.4	0.630
Utilization of support	6.8±2.0 ^a	7.6±2.1	0.043
Cells in peripheral blood			
Erythrocyte (10 ¹² /L)	3.4±1.2	3.8±1.8	0.460
Lymphocyte (0.00)	0.33±0.09 ^a	0.39±0.87	0.032
Granulocyte (0.00)	0.61±0.12	0.56±0.88	0.240
Monocyte (0.00)	0.04±0.01	0.06±0.05	0.900
Thrombocyte (10 ⁹ /L)	137.5±12.5 ^a	167.7±43.2	0.020
T lymphocyte subsets			
CD ₃ (0.00)	0.53±0.11	0.59±0.11	0.070
CD ₄ (0.00)	0.27±0.07	0.30±0.11	0.440
CD ₈ (0.00)	0.32±0.10	0.35±0.10	0.240
Natural killer			
CD ₅₆ (0.00)	0.26±0.11 ^a	0.29±0.11	0.041

^aP<0.05, ^bP<0.01, vs nondepression group.

DISCUSSION

Depression is a psychotic or neurotic condition characterized by inability to concentrate, insomnia, and feelings of extreme sadness, dejection and hopelessness, which commonly occur in cancer patients. It has been estimated that the incidence of severe depression in these patients is about 3%-50% depending on tumor site, stage, assessment methods, and a lot of other contributing factors, with an average overall incidence of approximately 20%^[18,26,27]. However, depression remains an often unrecognized source of suffering among cancer patients, which is partially because of the lack of recognition by clinical physicians. Under such circumstances, particularly when the depression was confused with symptoms resulted from the underlying disease, clinicians were usually inclined to dismiss even severe depression on the assumption that these "symptoms" are understandable^[27]. In fact, untreated depression in these patients might cause more frequent clinic visits, higher medical costs, longer hospital stay, as well as incompliance with therapeutic measures, poor quality of life, bad prognosis, and even accidental death^[20,28-32].

In the present study, we investigated the effects of depression on the parameters of cell-mediated immunity and its contributing factors in patients with cancers of the digestive tract. To our knowledge, it is one of the few clinical reports in recent years concerning depression in patients with digestive tract cancers. It was revealed that depression occurred in 50% of the cases, which was higher than the average total incidence among all tumor patients. Besides, there was also a higher percentage of cases with both SDS and SAS scores equal to or more than 50 in our study, accounting for 29.6% of the investigated patients. The exact reason for these has not yet been fully elucidated, it

is probably because the gut function relates so closely to people's daily life that a malignant disorder in the digestive tract might affect the psychological status of patients more easily compared with tumors of the other sites.

Lots of factors are closely related to the depression of cancer patients including physiological, immunological and psychosocial impacts. Although this correlation has been established as a whole in tumor cases^[33,34], however, little is known about the contributing factors to the depression in patients with cancer of the digestive tract according to the new bio-psycho-social model. Our study revealed that despite many factors such as cancer pain, poor economic status, tumor type, anorexia (X5), fatigue without apparent reasons (X10) might play a role, hyposexuality (X6), dispiritment (X1), agitation (X13), palpitation (X9), CD₅₆ and anxiety were the significant factors contributing to the depression of these patients by step-wise regression analysis.

Impairment of immunologic functions has been noted to be one of the major negative effects exerted by depression in cancer patients^[35]. Some immunological parameters such as T lymphocyte subsets and natural killer (NK) cells have been believed to be the major effectual mechanism against tumors^[36-43]. For instance, the growth of malignancies was inhibited by activated tumor-specific T cells^[44,45] and the depressed activity of NK cells was probably related to tumor enlargement and dissemination^[46]. Papadopoulos and his associates^[42] reported that the depletion of cytotoxic T cell (CD₈₊) and NK cell (CD₅₆₊) in advanced papillary ovarian cancer might in part explain the poor clinical outcomes of those patients. However, in our study, although significantly reduced NK cells (CD₅₆) and thrombocyte count were found in the depressive patients, T lymphocyte subset, CD₄/CD₈ ratio and other immunological parameters did not exhibit significant alterations between the two groups, suggesting that depression was probably not a necessarily factor leading to impairment of immune functions in patients with cancers of the digestive tract.

In summary, our study reveals that the incidence of depression is as high as 50% in patients with cancers of the digestive tract. Hyposexuality, dispiritment, agitation, palpitation, low CD₅₆ and anxiety are the significant factors contributing to the depression. Although significantly reduced NK cells (CD₅₆) and thrombocyte count are found in the depressive patients, T lymphocyte subset, CD₄/CD₈ ratio and other immunological parameters do not exhibit significant alterations between the depressive and non-depressive patients. Comprehensive measures including psycho-logical support therefore should be taken in order to improve their immunological functions, quality of life and clinical prognosis of cancer patients.

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