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INVESTIGATIVE REPORT

Association of Stress Coping Strategies with Immunological Parameters in Melanoma Patients

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In this exploratory case control study the association between stress coping strategies and lymphocyte subpopulations was calculated in 18 non-metastatic melanoma patients and 18 controls with benign skin diseases. Coping strategies were assessed using the German version of the stress-coping questionnaire (SVF 120). While in the control group patients showed significant negative correlations of lymphocyte subpopulations ($CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD45^+$ cells) with coping strategies that refer to defence, in melanoma patients significant positive correlations between lymphocyte subpopulations ($CD3^+$, $CD4^+$, $CD19^+$, $CD45^+$ cells) were found with regard to coping strategies that are characterized by diversion from stress and focusing on stress-compensating situations. The present data, in melanoma patients and controls, show contrary correlations between stress coping strategies and lymphocyte subpopulations. The interconnection between stress coping and immunologic alterations in malignant melanoma is a field deserving further multiprofessional investigation in order to provide new therapeutical approaches in the treatment and understanding of melanoma patients. ***Key words: melanoma; immune system; stress coping.***

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The incidence rate of cutaneous malignant melanoma has shown a significant increase in the past decades, whereas mortality rates seem to be stable in Europe (1, 2).

As a potentially lethal disease melanoma causes the majority of skin cancer-related deaths. When discovered at early stages, a high proportion of melanoma is curable with surgery and other treatment options but when detected after regional and systemic dissemination the prognosis becomes poorer (3). As cancer is essentially a life-threatening disease, its diagnosis and treatment is frequently accompanied by emotional distress (4, 5), which has a strong impact on physiological and immunological processes (6). Perceived psychosocial stress chronically stimulates the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis resulting in elevated salivary cortisol levels (7). These neuroendocrine processes also play an important role in the regulation of our immune system (8, 9). Several studies in humans as well as in animals show an interconnection between chronic and acute stress and the reactivity of the immune system, namely a significant change in cellular immune parameters such as natural killer (NK) cell cytotoxicity and T-cell activity (10–12).

In animal models the influence of chronic stress and UV radiation on the increase of susceptibility to squamous skin carcinoma was investigated, showing that stressed mice had a shorter median time to first tumour. In addition, subjects showed lower numbers of infiltrating $CD4^+$ cells, more regulatory/suppressor $CD25^+$ cells infiltrating tumours and more $CD4^+$ $CD25^+$ cells in the circulation (13), among other changes. Stress itself has effects on melanoma-relevant immunological parameters such as $CD3^+$, $CD4^+$ or $CD19^+$ cells. An analysis of the correlation between coping skills (Primary Appraisal Secondary Appraisal [PASA-] scale) and the expression of tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) showed higher expression of TNF-α and IL-6 between baseline and one hour post stress in subjects with a higher PASA "stress index". Hence one may conclude that an improvement in coping strategies and coping skills might influence the immunological response to stress in a positive way (14). Psychosocial stress contributes to a heightened vegetative load that is assumed to be associated with immunosuppression and cancer development and progression (7, 15, 16). To date very little is known regarding the reactivity of immunological parameters depending on social stress factors and psychological coping in persons who suffer from malignant melanoma. A few studies focused on the influence of psychosocial stress on tumour progression (15). It is not known to what extent stress-coping strategies are involved in immunological alterations. Recently, we were able to demonstrate, with parts of the present exploratory pilot study, that melanoma patients show an altered immunological reactivity to a standardi-

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zed mental stressor (17). The aim of the present analysis was to determine correlations between coping strategies and immunological parameters in melanoma patients compared to an age- and gender-matched control group of patients with benign skin diseases.

MATERIAL AND METHODS

Patients

Out of 38 outpatients, who were contacted between February and August 2011 and agreed orally and by written informed consent to participate in the study, we analysed 36 patients at the Department of Dermatology (Medical University of Graz). The patients were assigned either to a melanoma group (9 women and 9 men) with a mean age of 50.2 ± 13.3 years or an age-and gender-matched control group (9 women and 9 men) of benign skin lesions with a mean age of 50.3 ± 13.8 years. Because incomplete questionnaire data in one melanoma patient the latter and the corresponding control were excluded.

Melanoma patients attended an excision of the primary tumour or a re-excision after small excision of the primary tumour. All melanomas were primary, non-metastatic tumours with tumour thicknesses between 0.1 and 1.3 mm. The control group consisted of 18 patients with benign processes, i.e. naevi, epidermal and tricholemmal cysts, angioleiomyoma, scar, fibroma/neurofibroma, lipoma, sebaceous gland hyperplasia and condyloma acuminate. All patients participated in a defined test procedure in the morning of the planned surgery. Inclusion criteria: age from 18–75 years, approval to participation and written informed consent, sufficient compliance, and a good command of the German language. Insufficient compliance was a reason for exclusion.

The study was conducted in accordance with the human medical experimentation ethics document (Declaration of Helsinki 1964 and subsequent revisions). Approval was obtained from the ethics committee at Medical University of Graz, Austria. Anonymity was guaranteed by identifying each participant with an ID number.

Test procedure

All patients completed a defined test procedure including a mental standardized stress task with a period of rest before and after the stress task (17). Additionally, blood samples were taken before (baseline) and after the mental stress task.

The present paper particularly focuses on the immunological parameters at baseline (after a period of rest; duration: 10 min) and its association with stress-coping strategies in melanoma patients and benign controls.

Immunological parameters

The following immunological parameters were analysed: Lymphocyte subpopulations: $CD3^+$ cells, $CD4^+$ cells, $CD8^+$ cells, $CD16/CD56^+$ NK cells, $CD19^+$ cells and $CD4^+/CD8^+$ ratio.

Psychometric methods

German Stress-Coping Questionnaire (SVF 120). We used the German stress-coping questionnaire (SVF 120) to assess the coping strategies of melanoma patients and controls. The easily understandable SVF 120 evaluates coping strategies that are used during and after stressful situations. It consists of 120 items that are divided in 20 subtests. Each item offers the possibility to select the adequate answer within a 5-level rating scale. The questionnaire measures both positive and negative coping strategies. Positive strategies (POS_total) (trivialization, disparagement, defence from feeling of guilt, diversion from situation, substitute gratification, self-affirmation, relaxation, situation control, reaction control, positive self-instruction) effect efficient stress reduction and can be described as adequate coping strategies. Negative strategies (NEG_total) (escape, social withdrawal, intrusive thoughts, resignation, self-pity, self-blame) are associated with a stress-enhancing behaviour. Positive strategies can be divided in three subcategories: POS1, POS2 POS3. POS1 subsume subtests trivialization, disparagement, defence from guilt – strategies that refer to defence. POS2 include the strategies diversion from situation, substitute gratification, self-affirmation, and relaxation. This subcategory is characterized by diversion from stress and focusing on stress-incompatible situations. Subcategory POS3 (situation control, reaction control, positive self-instruction) focuses on the control of the stressor, the stress-associated reaction and the self-attribution of required competencies (18). Internal consistency coefficients (Cronbachs alpha) for the subtests vary between 0.66 and 0.92. The test is widely used and quality criteria are fulfilled (19). The SVF-120 takes 10–15 min to fill in and was presented as a paper pencil version.

Statistical methods

Associations between lymphocyte subpopulations ($CD3^+$ cells, $CD4^+$ cells, $CD8^+$ cells, $CD16/CD56^+$ NK cells, $CD19^+$ cells, $CD45^+$ cells, and CD4/CD8) and SVF 120 parameters were analysed for each group (melanoma group and control group) separately. These analyses were performed using nonparametric analysis (Spearman's correlation), since most of the parameters were not normally distributed and transformation (log) did not result in a normal distribution. Due to the exploratory nature of this pilot study alpha-adjusting was not undertaken.

RESULTS

Correlations between immunological parameters and stress coping strategies

While in the control group significant correlations were found with regard to lymphocyte subpopulations with POS1, in melanoma patients significant correlations were found with POS2. Only in melanoma patients these correlations resulted in significant correlations with POS_total. In the control group all analysed lymphcytes except $CD16/CD56^+$ NK cells and CD4/CD8 ratio showed negative associations with POS1 ranging from $\rho = -0.694$ ($p = 0.001$) to $\rho = -0.538$ ($p = 0.021$). In the melanoma group all analysed lymphocytes except $CD8^+$ cells, $CD16/CD56^+$ NK cells and CD4/CD8 Ratio showed positive associations with POS2 ranging from $\rho = 0.685$ ($p = 0.002$) to $\rho = 0.629$ ($p = 0.005$) and POS_total ranging from $\rho = 0.608$ ($p = 0.007$) to $\rho = 0.559$ ($p = 0.016$). In both groups no significant correlations could be observed between lymphocyte subpopulations and NEG_total. Table I lists the correlation of stress-coping strategies with immunological parameters within the melanoma group and controls.

Table I. *Correlation between immunological parameters and stress-coping strategies shown using Spearman correlation coefficients*

	Control group					Melanoma group				
	POS1	POS2	POS3	POS_total	NEG_total	POS1	POS2	POS3	POS_total	NEG_total
$CD3^+$ cells	**–0.638****	0.155	–0.197	–0.281	0.075	0.193	**0.629****	0.38	**0.562***	–0.098
$CD4^+$ cells	**–0.552***	0.302	–0.144	–0.176	0.104	0.198	**0.685****	0.365	**0.559***	–0.011
$CD8^+$ cells	**–0.655****	0.040	–0.287	–0.348	0.057	0.135	0.237	0.236	0.364	–0.119
$CD16/CD56^+$ NK cells	–0.412	–0.108	–0.199	–0.328	–0.205	0.044	0.192	0.032	0.027	–0.224
$CD19^+$ cells	**–0.538***	0.26	–0.203	–0.214	0.056	0.373	**0.634****	0.394	**0.608****	0.005
$CD45^+$ cells	**–0.694****	0.076	–0.205	–0.353	0.240	0.196	**0.665****	0.376	**0.570***	–0.086
CD4/CD8 ratio	0.213	0.114	0.179	0.176	0.084	0.037	0.234	–0.051	–0.008	0.079

*$p<0.05$; **$p<0.001$. POS1, POS2, POS3: Subcategories of positive strategies; POS_total: positive strategies; NEG_total: negative strategies.

DISCUSSION

In melanoma as well as in control patients we found correlations between different lymphocyte subpopulations and stress-coping strategies. Positive, stress reducing coping strategies correlated positively with $CD3^+$, $CD4^+$, $CD19^+$ and $CD45^+$ cells at baseline. This effect was found in the melanoma group, but not in controls. In controls however, negative correlations between positive stress-coping strategies and $CD3^+$, $CD4^+$, $CD8^+$. $CD19^+$ and $CD45^+$ cells were observed. Thus, we can notice that in benign controls high values of coping strategies that focus on diversion from stress and generating stress-incompatible situations are associated with lower counts in specific lymphocyte subpopulations. In contrast, melanoma patients who predominantly cope with stress using coping strategies that focus on defence, have lower values in certain lymphocyte subpopulations. In our analysis melanoma patients show divergent correlations of positive stress-coping subcategories than controls. Regarding the influence of coping strategies on disease progression previous studies showed that the course of disease is determined and influenced by neuroendocrine and psychological factors, health behaviour, and compliance, which ultimately have an impact on the immune system (5). There is strong evidence deriving from the existing literature that chronic and acute psychosocial stress contribute to disturbances within the neuroendocrine, the immune and the autonomic nervous system of the human body (9, 20). Acute and chronic psychosocial stress can induce considerable changes in innate and adaptive immune responses. These changes are predominantly provided via neuroendocrine mediators from the HPA and the sympathetic-adrenal axis (6, 21). Besides the ability to signal to the brain to induce neurochemical and neuroendocrine changes, specific cytokines, also called the "hormones" of the immune system, play an important role in various activities of the central nervous system such as neuro-immunological and behavioural changes (22). With regard to IL-1, IL-6 and TNF-α studies in humans and in animals revealed an association with the activation of the HPA axis (23–25) and a possible modulation of the hypothalamic-pituitary thyroid and the hypothalamic-pituitary-gonadal axis, findings, which support the hypothesis of an existing correlation between the immune system and the endocrine system (26). Thus it is conceivable that psychosocial stress and unfavourable stress coping might influence these systems in an adverse way (22). Strong scientific-based evidence is given that an equivalent to the HPA axis using the same signalling molecules exists in the skin. This local skin-stress-response system also employs corticotropin releasing hormone (CRH) acting on locally expressed CRH receptors, which supports the hypothesis of an existing skin-related neuroendocrine pathway (27, 28). In a recently published article, Kim and colleagues (29) reviewed the functioning of the central and the peripheral, skin-associated HPA axis in different stress-related skin diseases. Besides the fact that the HPA axis hormones are mainly involved in the carcinogenesis, tumour development and tumour progression, chronic stress leads to suppression of skin-related cell-mediated immunity and to a reduction of circulating leukocytes counts due to an HPA axis activation. In melanoma cell lines, the stress hormones CRH, adrenocorticotropic hormone (ACTH) and alpha-melanocyte-stimulating hormone (alpha-MSH) were found to be strongly expressed, in contrast to normal and haematological malignant cells (30). Furthermore it was shown that notably melanoma and squamous cell carcinoma revealed strong immune reactivity for CRH, as well as strong expression of ACTH and alpha-MSH (30). One may conclude that an accompanying intervention on a psychosocial level in terms of psychotherapy or concomitant behavioural therapy (31, 32) such as improvement of coping styles may be beneficial for the disease outcome and the well-being of cancer patients (33–36).

A limitation of the present study is that the small sample size does not allow the creation of subcategories (e.g. tumour thickness or subtype of melanoma) that could eventually detect further aspects that explain the inverse association of positive strategies and immunological parameters.

In terms of biopsychosocial medicine, besides surgical and pharmacological interventions, the improvement of stress-coping strategies is a possible key to modulate the autonomic nervous tone and consequently the endocrine and immune system. The interconnection between stress coping and immunologic alterations in malignant melanoma is a field deserving further investi-

gation in order to provide new therapeutical approaches in the treatment of melanoma patients.

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