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Serum Selenium in Melanoma and Epidermotropic Cutaneous T-cell Lymphoma

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As several studies have demonstrated a relationship between decreased serum selenium concentrations and the frequency of certain cancers, we studied these concentrations in two kinds of cutaneous tumour cancer: melanoma and epidermotropic cutaneous lymphoma. We first determined the predictive value of the selenium assay for the frequency of recurrences in stage I and II melanomas and then considered the relationship between serum selenium concentrations before treatment and therapeutic response. Two hundred melanomas (81 stage I, 63 stage II, 56 stage III) and 51 epidermotropic cutaneous T-cell lymphomas (CTCL) (8 stage I, 24 stage II, 10 stage III, 9 stage IV) were included in the study. Selenium assays were performed by atomic absorption spectrophotometry (92 ± 16 μg/l in 30 normal subjects). Our study showed decreased serum selenium concentrations for melanoma (81 ± 27 μg/l) and lymphoma (78 ± 36 μg/l) relative to disease severity. The concentration was significantly lower (76 ± 22) for stage I and II melanomas with recurrence within 2 years (31 patients), compared to those without recurrence (113 patients) ($p < 0.05$). Before treatment, it was higher in CTCL with good response to treatment (89 ± 36) than in those without response (62 ± 30) ($p < 0.01$). This study thus demonstrates the prognostic value of selenium assays in the follow-up of melanoma and CTCL.

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In cancer pathology, the preventive role of selenium, a trace element, has been demonstrated in animal experiments in numerous species as well as in extensive epidemiological studies in man (1,2), showing an inverse relationship between environmental selenium and the frequency of certain cancers: the lower the selenium level in the environment (and consequently in food) in a given country or region, the lower the mean concentration of serum or plasma selenium in the population and the higher the rate of cancer mortality. The most frequent cancers in selenium-poor regions are colic and rectal carcinomas. However, the effect is apparently not the same for all cancers since some authors have noted a significant serum selenium decrease in carcinoma of the urinary bladder, kidney, face, neck and lung (3).

The best known biochemical function of selenium is to serve as a cofactor of glutathione peroxidase (GSH-Px). This enzyme, localized in the cytosol and the mitochondrial matrix (4), is tetrameric and contains a selenocysteine radical (the active site of the enzyme) in each subunit. The major role of GSH-Px is to maintain sufficiently low levels of hydrogen peroxide (H_2O_2) as well as lipidic hydroperoxides (ROOH) likely to form in the cell. GSH-Px, in association with superoxide dismutase (SOD) and catalase, is thus part of the cell enzymatic system preventing formation of free radicals. A decrease in serum selenium is associated with reduced GSH-Px activity and can lead to the formation of potentially carcinogenic toxic substances (3). In addition, animal experiments and cell cultures have shown that selenium has an immunomodulation effect (3–5), with increased antibody synthesis and N-killer cell activity as well as direct alteration of cancer cell metabolism (6).

These different data in the literature led us to study serum selenium concentrations in two types of skin tumours: melanoma and epidermotropic cutaneous T-cell lymphoma (CTCL).

MATERIALS AND METHODS

Patients and controls

Patients. The study was carried out in patients with diagnosed and histologically confirmed malignant melanoma or CTCL before treatment and followed up by the Department of Dermatology. Two hundred patients (103 women, 97 men; mean age 53 years, range 8–81) had malignant melanomas: 81 stage I (localized skin tumour), 63 stage II (nodal metastases) and 56 stage III (visceral metastases). Fifty-one patients with epidermotropic CTCL (16 women, 35 men; mean age 58 years, range 20 – 82) were rated according to the Scandinavian classification (7) as stage I (8), II (24), III (10) or IV (9). Clinical follow-up was carried out for 2 years to evaluate, in stage I and II melanomas, the appearance or absence of nodal or visceral recurrences, and therapeutic response for stage III melanomas and lymphomas. Melanoma (stage III) received chemotherapy (Deticene, Vindesine or Fotemustine) combined with interferon α, and epidermotropic CTCL received interferon α alone or combined with retinoids.

Patients were thus classified in two groups according to the clinical course of their disease under treatment: responders (complete or partial response) and non-responders (stability or progression). For melanoma stage III, complete response was the disappearance of metastatic lesions, partial response a decrease of more than 25% of the size of metastatic lesions; stability was a decrease less than 25% of the size of metastatic lesions or no decrease and finally progression was an increase in the size of metastatic lesions. For CTCL the response to treatment was evaluated clinically and histologically. A complete response was defined as the disappearance of all signs of disease activity for at least 4 weeks. No patient has received chemotherapy before the dosage of selenium, and other therapies (interferon α, retinoids, and PUVA-therapy) were stopped for at least 4 weeks.

Controls. As serum selenium concentrations are subject to geographical influence, assays were performed on sera from 37 normal subjects (19 women, 18 men; mean age 55 years, range 30–69) living in the same region as the patients in order to obtain a corresponding loco-regional population with no current or previous tumoral pathology.

Serum selenium determinations

Samples were obtained in tubes specially treated for trace-element assays which were performed using a Perkin-Elmer electrothermic atomic absorption spectrophotometer with Zeeman effect. Results are expressed in μg/l. For each patient blood samples were taken at the time of diagnosis of the stage.

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Statistical analysis

Student's t-test was used.

Results are expressed as mean ± standard deviation (SD). For correlation analysis the Spearman correlation coefficient was used.

RESULTS

Serum selenium measured in patients with malignant melanoma (81 ± 27 μg/l) or CTCL (78 ± 36 μg/l) was decreased compared to controls (92 ± 16 μg/l) ($p < 0.001$). For both melanomas and epidermotropic CTCL, there were no significant differences related to sex or age (lymphomas < 50 years = 79 ± 25 μg/l, > 50 years = 81 ± 21 μg/l; melanomas < 50 years = 78 ± 23 μg/l, > 50 years = 82 ± 27 μg/l). However, there was a significant difference ($p < 0.05$) for Breslow's thickness (< 1.5 mm = 85 ± 30 μg/l; > 1.5 mm = 76 ± 28 μg/l).

For both melanomas and lymphomas, a progression in disease stage was associated with a decrease in selenium.

For melanomas, the difference was highly significant between controls (92 ± 16 μg/l) and stage II (77 ± 27 μg/l) or III (75 ± 26 μg/l) ($p < 0.001$) as well as between stage I (88 ± 26 μg/l) and stage II ($p < 0.02$) and III ($p < 0.01$). There was no significant difference between controls and stage I or stages II and III.

For epidermotropic CTCL, there were no statistically significant differences between controls and stages I and II (85 ± 35 μg/l), whereas the selenium concentration for stages III and IV (68 ± 34 μg/l) was significantly decreased compared to controls ($p < 0.001$).

In terms of the clinical course of melanomas, mean serum selenium concentration in patients with recurrences (76 ± 22 μg/l) was significantly lower compared to those without recurrences (86 ± 28 μg/l) ($p < 0.05$) both in stage I and II. However, there was no significant difference according to treatment response at stage III (non-responders 76 ± 27 μg/l, responders 73 ± 25 μg/l).

The clinical course of epidermotropic CTCL showed a highly significant difference between selenium concentrations before treatment in responders to treatment (89 ± 36 μg/l) and non-responders (62 μg/l) ($p < 0.01$) not related to the stage of the illness. Compared to controls, the selenium concentration of responders was practically normal, whereas that of non-responders was markedly decreased ($p < 0.001$).

DISCUSSION

This study concerning the course of two types of skin lesions shows an inverse correlation between clinical stage and serum selenium concentration: the more advanced the disease stage, the lower the selenium level both for melanoma and epidermotropic CTCL. Statistical studies in cases of epithelioma (8) and malignant melanoma (9) have shown a significant decrease in serum selenium concentrations according to stage. Our results for melanomas are in general agreement with those of Reinhold et al. (9). Unlike us, they found a difference between controls and stage I, and between stages II and III, whereas we noted a significant difference between stages I and II not found in their study. They also found a sex-related difference in the patient population, with higher selenium concentrations in men.

A decrease in serum selenium concentrations in cases of epidermotropic CTCL has not previously been demonstrated, although it may be correlated with the decreased GSH-Px activity reported by Juhlin et al. (10) for mycosis fungoides.

To date, no study has shown a relation between serum selenium concentrations and skin cancers at mid-course. For stage I and II melanomas, the present study indicates a relation between decreased serum selenium levels and increased risk of recurrence. After a follow-up of more than 24 months in some cases, our results indicate the apparent "prognostic" value of serum selenium levels for the frequency of recurrence of stage I and II melanomas.

Concerning therapeutic response to treatment, no selective value for selenium was found in the case of stage III melanomas. However, for epidermotropic CTCL, a low selenium concentration was associated with a poorer therapeutic response with a uniform distribution of clinical stages according to the response.

Animal experiments have already demonstrated the protective role of selenium with respect to skin cancers. In the mouse, a selenium supplement in feed protected against the development of tumours induced by chemical agents (3, 11) or ultraviolet radiation (12). Moreover, the last study showed the existence of a dose-effect relationship between selenium concentration and the frequency of skin cancers induced by ultraviolet B radiation. It is also noteworthy that ultraviolet radiation can reduce skin glutathione levels (13, 14).

An important point concerns the fact that some tumours seem to concentrate selenium. Thus, studies have been carried out to determine the possibility of using selenium as a localizing agent for brain tumours (15). In this respect, the decrease in serum selenium concentration associated with cancers might be considered as a result of the disease alone rather than as a prognostic risk factor. However, a significant decrease in serum selenium has been demonstrated in studies concerning epitheliomas (8) and stage I melanomas (9). Given the small size of these tumours, the studies strongly suggest that the selenium decrease was not due to the tumour itself.

It may be concluded that the results of this study, together with those of 8 numerous epidemiological studies demonstrating the relation between a selenium-poor environment and food supply and increased cancer mortality and those of animal studies showing the protective role of serum selenium, provide evidence of the possible role of this trace element in the prevention of cancer pathology. Some cancer-preventive protocols already associating a selenium food supplement with classical treatments provide doses of up to 200 μg/day or even more. Nevertheless, due caution should be observed since excessive selenium intake may induce certain tumours (3, 6, 16).

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