The Relation between Seborrheic Keratoses and Malignant Solid Tumours
A Case-control Study

JEAN JACQUES GROB1, MARIE CHRISTINE RAVA1, JOANNY GOUVERNET2, PIERRE FUENTES2, LUCIEN PIANA2, MARC GAMERRE2, JEAN CLAUDE SARLES1 and JEAN JACQUES BONERANDI1

1Service de Dermatologie, Hôpital Ste Marguerite, 2Laboratoire de Statistique, Faculté de médecine Timone, 3Service de Chirurgie Thoracique, Hôpital Ste Marguerite, 4Service de Gynécologie, Hôpital de la Conception and 5Service de Chirurgie Digestive, Hôpital Ste Marguerite, Centre Hospitodier-Universitaire, Marseille, France

In order to establish whether or not there is an association between cancer and intense growth of seborrheic keratosis, the so-called Leser-Trelat sign, we conducted a case control study in which the number and features of seborrheic keratosis in 82 patients with recent solid tumours, were compared with 82 age- and sex-matched controls. Neither numbers nor features of seborrheic keratosis differed significantly in patients and controls. Eruptive seborrheic keratosis was noted in only one patient and one control. This study showed that solid malignancies are not generally associated with an increase in the number or size of seborrheic keratosis lesions, thus suggesting that they are not controlled by a hypothetical secretion of growth factors by tumours. Our results suggest that Leser-Trelat is either a coincidence, or at most a very rare sign of unusual types of cancer. We also showed that multiple cherry angiomas, previously reported to be a paraneoplastic sign, are not regularly associated with solid tumours. Key words: Cancer; Paraneoplastic sign; Seborrheic warts; Angiomas.

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J.-J. Grob, Service de Dermatologie, Hôpital Ste-Marguerite, 13277 Marseille Cedex 09, France.

Leser-Trelat sign (1,2) is one of the cutaneous paraneoplastic syndromes. It corresponds to the sudden appearance of large numbers of seborrheic keratoses (SK) and/or, at least, rapid increase in the number or size of SK, in association with a malignant tumour.

Perusal of the literature showed that cutaneous signs are often a precursor to internal malignancy. Although no tumour type was consistently associated with the Leser-Trelat sign, adenocarcinoma was frequent. SK generally exhibit no particular pattern, but Heng et al. (3) recently reported a linear arrangement of SK in 5 patients with colonic cancer. Pruritus is often noted (4). Occurrence of SK current with angiomas has been reported (5, 6), but this seems rare.

The credibility of this skin change as a paraneoplastic sign has rightly been called into question (7) for several major reasons. First, SK are a far more common disorder than other paraneoplastic dermatoses, such as acanthosis nigricans or Bazex syndrome. Second, in most cases, remission does not occur after successful cancer therapy. Third, there is no proof of an increased association between Leser-Trelat sign and any specific type of cancer. Investigation of the physiopathologic mechanisms underlying the Leser-Trelat sign has led to the hypothesis that SK are stimulated by growth factors secreted by tumours. Although no formal proof of this has been obtained, elevated urine EGF (8) and alpha TGF (9) values were reported in 2 cases. In 2 other cases, EGF was not high (10, 11).

If we assume that many tumours do secrete growth peptides and that SK can be stimulated by them, it would be reasonable to suspect that an increase in the number and size of SK ought to occur in a wide range of malignant diseases. Leser-Trelat sign could therefore be merely the "visible tip of the iceberg". In other words, cancer may frequently be associated with an increase in SK which goes unnoticed unless it is sudden and massive as in the form of Leser-Trelat sign.

In order to show whether or not there was an association between cancer and intense growth of SK, we conducted this case-control study, comparing the numbers and features of SK in healthy subjects and in patients with recent solid tumour growth. The only previous study on this topic (12) compared 36 cancer patients and 36 controls. No difference was noted in the distribution and density of SK. However, since the number of patients was low, counts on the whole body were semi-quantitative, and only adenocarcinomas (31 in 36 patients) were considered, these findings need confirmation.
Table I. Histological diagnosis in 82 patients with malignant tumour

| Adenocarcinoma (39) | Breast 16 | Stomach 4 | Colon 7 | Rectum 3 | Pancreas 2 | Liver 2 | Thyroid 1 | Ovary 1 | Uterus 3 |
| Squamous cell carcinoma (34) | Larynx 1 | Lung 23 | Esophagus 10 |
| Others (9) | Melanoma 8 | Thymoma 1 |

as coexistence of pruritus were also noted. Acanthosis nigricans and the presence of multiple cherry angiomas (Campbell De Morgan spots) were systematically sought.

Statistical study

The proportions of subjects with or without SK in the cancer and control groups were compared using the matched $\chi^2$-test. Comparison between numbers of SK in cancer and control groups was carried out by applying the Wilcoxon test. In the cancer group a Mann-Whitney test was used to study the number of SK as regards tumour type. Proportions of patients and controls with and without small cherry angiomas were compared by matched $\chi^2$-test.

RESULTS

Mean age in the patient group was 60.6 years (range: 40 to 80 years, SD = 10.4) and 60.3 years (40 to 82 years, SD = 11.1) in the control group. Each group comprised 49 men and 33 women. Tumour types are listed in Table I.

The proportion of subjects presenting SK (Table II) did not differ significantly between the control and the cancer group (matched $\chi^2$, $p=0.61$). No significant difference was noted in number of SK (Tables II and III) between the control and cancer groups. This was true for SK1, SK2, SK3, and SK3, wherever these counts were made, i.e. over the whole body, on usually exposed areas and on rarely exposed areas (Wilcoxon test, $p=0.46$).

When the 39 patients with adenocarcinomas or the 43 with other tumours were respectively compared with their 39 or 43 matched controls, no significant difference was found in SK counts (Wilcoxon test, $p=0.13$). Numbers of SK (SK1, SK2, SK3, SK3) over the whole body did not differ significantly in the patients with adenocarcinomas vs those with other tumour types (Mann-Whitney test, $p=0.10$). We must, however, mention that for counts of SK2 on areas regularly exposed to the sun, the degree of significance was 0.06. A study involving larger populations might have shown that patients with adenoc.
carcinomas have fewer SK2 on sun-exposed areas than those with other tumour types.

A linear pattern was noted in 1 patient with cancer and 2 controls. Pruritus was observed in 1 control. Sudden onset of SK was observed in 1 patient and 1 control. Twenty-nine patients and 21 controls had numerous small cherry angiomas, but the difference was not significant ($\chi^2$, p≥0.07).

**DISCUSSION**

We found no relationship between the presence of a solid tumour and the number, size, macroscopic features or mode of onset of SK. Our results do not suggest that the Leser-Trelat sign constitutes an extreme form of a frequent phenomenon in cancer patients.

The possible sources of bias in this study are few. Diagnosis of SK, which is generally readily identifiable by an experienced dermatologist, was based solely on clinical evidence. Although some small SK with smooth surfaces (SK1) could have been confused with senile lentigos or solar keratoses and vice versa, results obtained with SK1 are in line with those obtained with large verrucous SK (SK2, SK3) for which confusion is unlikely. The cancer and control groups were matched only for age and sex, but study of factors potentially influencing SK (age, sex, phenotype, and sun exposure) in a group of normal patients showed that only age was of any importance (to be published).

Our findings do not rule out an association between SK and cancers other than solid tumour. However, Leser-Trelat sign has seldom been reported with lymphoma or leukemia. Since our study involved a variety of tumour types, it does not rule out a relation between an increase in SK and a particular tumour type, but the diversity of internal malignancies reported with Leser-Trelat sign does not corroborate this hypothesis. Furthermore, although the most frequently reported tumour-type with Leser-Trelat sign is adenocarcinoma, our statistical data suggest that a larger study might show that individuals with adenocarcinomas have fewer SK2 on usually exposed areas than do those with other tumours.

Sudden onset of SK was noted by 1 control and 1 patient. This is apparently a rare phenomenon which does not seem to be specific for cancer. It may be speculated that Leser-Trelat sign results from an accidental concurrence of two events that are rare but not exceptional after 40 years, viz. cancer and eruptive SK. In this regard it should be noted that most subjects questioned for this study ignored their SK. An eruption of SK is much more likely to be noticed by a patient who knows that he has a cancer than by a subject who has no reason to be alarmed. This could partly explain the Leser-Trelat sign.

This study showed that solid tumours are not generally associated with an increase in the number or size of SK. Thus in most patients with solid malignancies, SK do not appear to be controlled by a hypothetical secretion of growth factors by the tumour. However, as eruptive SK was very unusual both in cancer and in control groups, our study could not determine whether Leser-Trelat sign is a rare marker of some unusual cases of malignancy or only a coincidence. The only way to rule out the latter possibility would be to compare the incidence of cancer in people with eruptive SK and in controls. Lastly, our results also suggest that multiple cherry angiomas previously reported as a paraneoplastic sign (13) are not regularly associated with solid tumours.
Increased Plasma Norepinephrine in Psoriasis

GRUIA IONESCU and REINHOLD KIEHL

Research Department, Spezialklinik Neukirchen, Neukirchen, West Germany

Free plasma catecholamines were measured by means of a standardized HPLC method in 50 adult patients with psoriasis and in 18 healthy volunteers. The concentrations of circulating norepinephrine were significantly higher in the psoriasis group (p < 0.005); by contrast only slight differences were found in the epinephrine and dopamine concentrations. The possible mechanisms leading to these changes are discussed. Key words: Psoriasis; Norepinephrine; High-performance-liquid-chromatography.

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G. Ionescu, Spezialklinik Neukirchen, 8497 Neukirchen, West Germany.

We have recently published two reports describing increased plasma norepinephrine concentrations in severe atopic eczema (1, 2). Similar results were noted by us in patients with acute allergic asthma, a finding already reported by others (3). Finally we came to the conclusion that a large part of the elevated neurotransmitter may be released from the sympathetic by a disturbed regulatory mechanism (2).

Enhanced sympathetic activity may lead to immune changes (4) and worsening of the clinical picture. Physiological norepinephrine release and availability seem to be important for normal T cell (and possibly B cell) function (5). We therefore raised the question: might immunobiological changes in psoriasis (6, 7) be related to increased norepinephrine levels. To tackle this question, we investigated the in vivo state of plasma catecholamines in patients with psoriasis and in healthy controls by means of a sensitive high-performance-liquid-chromatography (HPLC) method.

MATERIAL AND METHODS

Fifty adult patients (age range 17-45 years) with clinically proved psoriasis vulgaris (8) with more than 5 years' disease history, as well as 18 healthy volunteers having no history or sign of a skin disorder (age range 16-40 years) agreed to participate in this study. All patients avoided oral and topical corticosteroids and/or phototherapy for at least 2 months.

Venous blood samples were taken on Na-EDTA in the supine position at 9 a.m. after 10 min of bed rest. The concentration of plasma catecholamines was determined by reverse-phase HPLC with electrochemical detection (9). Chromatographic separation was carried out on a C-18 plasma catecholamine column (5 × 150 mm, spherical particle size: 5 μm) after Al2O3 extraction. Equipment, standardized method and reagents were supplied by Waters,

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