The Relation between Seborreic Keratoses and Malignant Solid Tumours

A Case-control Study

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In order to establish whether or not here 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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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, a 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 concurrent 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 in 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

MATERIAL AND METHODS

Subjects

The case-control study material comprised 82 patients and 82 matched controls. The patients were over 40 years of age and had had solid tumours diagnosed within the previous 3 months. They had no history of cancer (except basal cell carcinoma) and had not yet undergone radiotherapy or chemotherapy. The 82 controls were selected from among outpatients consulting at the Hôpital Sainte Marguerite, excluding those consulting for dermatologic disorders or malignant diseases and those with severe debilitating disorders. They were matched with the patients with regard to age (maximum deviation: 6 years) and sex.

Methods

SK counts were made by the same physician in both groups. Separate counts were made for the total number of SK (SKt), number of SK smaller than 5 mm in diameter or superficial SK (SK1), number of verrucous SK larger than 5 mm (SK2) and number of exuberant SK (SK3). Separate counts were made because controls and cancer patients can differ not only with regard to the number of SK but also to their mophology and size. Each count was performed over the whole body, on areas usually exposed to the sun and on areas rarely exposed to the sun. Pattern, i.e. linear or zonal, and mode of onset, i.e. indolent or sudden, as well 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 χ^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 χ^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 χ^2, $p \geq 0.61$). No significant difference was noted in number of SK (Tables II and III) between the control and cancer groups. This was true for SKt, SK1, SK2, and SK3, wherever these counts were made, i.e. over the whole body, on usually exposed areas and on rarely exposed areas (Wilcoxon test, $p \geq 0.46$).

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, $p \geq 0.13$). Numbers of SK (SK1, SK2, SK3, SKt) over the whole body did not differ significantly in the patients with adenocarcinomas vs those with other tumour types (Mann-Whitney test, $p \geq 0.10$). 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 adeno-

Table II. *Distribution of patients and controls according to number of seborrheic keratosis on overall body*

	Number of SKt on overall body				Number of SK2 on overall body		
	0	≤5	6 to 10	>10	0	≤5	>5
Number of patients (n=82)	28	30	8	16	47	25	10
Number of controls (n=82)	32	24	11	15	53	16	13

Table III. *Distribution of patients and controls according to number of seborrheic keratosis on sun-exposed areas.*

	Number of SKt on sun exposed areas				Number of SK2 on sun exposed areas		
	0	≤5	6 to 10	>10	0	≤5	>5
Number of patients (n=82)	49	24	6	3	65	15	2
Number of controls (n=82)	50	25	3	4	53	16	13

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 in 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 (χ^2, $p \geq 0.07$).

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 keratosis 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 adenocaricinomas 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 malignany 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.

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