Short communication

CUTANEOUS PARANEOPLASTIC SYNDROMES
Attempt of a New Classification

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ABSTRACT

A new classification of dermal paraneoplasias is proposed, which could be helpful in the search for responsible agents. Dermal paraneoplasias are differentiated into 3 groups. The first displays a hyperfunction of certain components of the skin, the second is characterized by hyperplasia of the skin compartments, the third one includes disorders that are triggered by immunological factors.

KEY WORDS:
cutaneous paraneoplastic syndromes, paraneoplastic dermatoses, new classification

INTRODUCTION

Since Trousseau defined the first paraneoplasia (1), superficial migratory thrombophlebitis in 1861, many other skin sings have been reported that are closely connected to visceral cancer. To specify this inhomogenous group of syndromes it is necessary to define the term paraneoplasia. Probably the best definition fitting also other noncutaneous paraneoplasias, is that of Delacretaz (2): "The cutaneous paraneoplastic syndromes (CPS) are nonmetastatic manifestations which are a result of the existence of a malignant visceral tumor and/or diseases of the lymphoma group especially leukemias. The close connections between a dermatosis and tumor are recognized by the disappearance of the until then scarcely or not at all influenced skin disease, if the malignant tumor is eliminated by operation, radiation or cytochemical therapy. The recurrence of the skin signs indicates a relapse of the tumor or metastases,"

Many efforts were made in the past to classify the paraneoplastic syndromes. Herzberg (3), one of the best experts in that field in Germany, wrote 1980 in his book: "It is extremely difficult, if not to say impossible to draw up a classification of the CPS based on logical principle. "He concluded that the dermatoses are too heterogeneous and that there are open points in the definition. A classification of CPS that depends on how close the connection of the dermatosis and the tumor is, is currently in use. This classification fits such syndromes as hypertrichosis lanuginosa acquisita(HLA),

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Torre-Muir's syndrome and other syndromes that are closely connected to a internal malignancy, but not diseases like erythrodermia, pruritus– or other signs that only sometimes point to a underlying cancer disease. Specifically, this classification doesn't consider the mechanisms which enable the cancer to provoke these skin symptoms.

PROPOSAL FOR A NEW CLASSIFICATION

In contrary to what has been said we would like to propose a new classification of CPS that will lead to consideration of possible tumor causing such skin lesions.

We suggest that there is a group of CPS that is associated with hyperfunction of various skin elements (Table 1). Such syndromes are: acanthosis nigricans-hyperkeratosis (also seen in other hyperkeratotic paraneoplasias), neoplastic Addison's disease-hyperproduction of melanin and to some extent hypertrichosis lanuginosa acquisita-formation of hair due to excretion of trichokeratin. In these syndromes of hyperfunction, hormones or hormone-like agents presumably play a major role in stimulating an organ or parts of it to excrete a certain compound. These agents are probably hormone-like peptides (4). The agent in HLA that stimulates hair growth is not fully known, but according to own observations it could be an acid mucopolysaccharide (5). In 1961 Meyer et al. reported the hair growth enhancing effects of acid mucopolysaccharides (6). They have seen the strongest reaction with heparitin-sulphate, followed by chondroitin-sulfate.

The hyperfunction separate these paraneoplasias from another group of paraneoplastic syndromes that are characterized by a hyperplasia of special skin compartments. Such Syndromes are: Torre-Muir syndrome-growth of sebaceous glands and parts of hair follicles, Cowden syndrome-growth of connective tissue, multiple endocrine neoplasia syndrome-growth of skin nerves, Carney syndrome-growth of melanocytes and other syndromes (7).

This group of CPS is most likely triggered by special growth factors. The epidermal growth factor, for example, can inhance tumor induction in the skin (8), In cases of Leser-Trelat sign several authors proved the influence of growth hormones and alfa transforming growth factor (9,10). It is not only the epidermal growth factor, which is involved in paraneoplasias, as it was shown in cases of Torre's syndrome (11). There are most probably other factors that could influence further skin compartments.

In this proposed classification of the paraneoplasias, those associated with a hyperplasia represent mostly geno-dermatoses, wheres those characterised by hyperfunction represent sporadic cases. Only HLA is an exception because it has both: hyperfunction (long hairs) and hyperplasia (new hair germs). If HLA would be a genodermatosis, there should be a family increase in cancer and subsequently the occurrence of typical skin markers. The family history is mentioned only once in the HLA literature (12) with no history of excessive facial or body hair, or multiple internal malignancies. But one should keep an eye on the families to become aware of possible genetic accumulation. In HLA we need to look for two compounds because of its complex expression. There should be a growth factor enhancing new hair bulbs as well as a possible hormone stimulating the hair follicles to produce hairs.

The third group of syndromes are the inflammatory or immune triggered skin disorders, such as glucagonoma syndrome, erythema gyratum repens, dermatomyositis and many others (Table 1). This group includes the largest number of skin diseases and is therefore somewhat inhomogeneous. That will possible change in the future as the triggering factors are possible to detect biochemically and biologically. We know for instance, that many carcinomas can produce hormones. In most instances these hormones are different from physiological hormones (13). These varieties are regarded as prohormones. Such prohormones can act as neoantigens in the body, because these substances are not known to the immune system. Physiologically prohormones are intracellular intermediate stages of hormones.

In every respect it is essential to prove the substances that are released by the carcinoma. They could serve in the future as qualitative and quantitative tumor markers or as possible therapeutic agents e.g. in alopecia. For this reason we prefer the classification based more on cancer products than on tight connections of the carcinoma and the skin signs.

Table 1. Proposed classification of cutaneous paraneoplastic syndromes (CPS)

1. CPS with hyperfunction probably caused by hormone-like peptides
   - Acanthosis nigricans
   - Howel-Ewans syndrome /keratoderma with carcinoma of oesophagus/Mucinosis follicularis
   - Melanodermias
   - Acrokeratosis Basex /paraneoplastic acrokeratosis/
   - Scleromyxedema
   - Amyloidoses
2. CPS with hyperplasia caused by various growth factors
   - Torre-Muir syndrome /sebaceous neoplasia and visceral carcinoma/
   - Gardner syndrome /epidermoid cysts, polyposis of the colon and fibromas of the skin/
   - Carney syndrome
   - Cowden syndrome /multiple hamartoma disease/
   - Multiple endocrine neoplasia syndrome
   - Birt-Hoggh-Dube syndrome
3. CPS triggered off by immunological factors
   - Erythema gyratum repens
   - Dermatomyositis
   - Erythrodermia
   - Bullous dermatoses
   - Glucagonoma syndrome
   - Sweet syndrome /acute febrile neutrophilic dermatosis/
   - Various erythemas
   - Vasculitis

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