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THE ROMBO SYNDROME: A FAMILIAL DISORDER WITH VERMICULATE ATROPHODERMA, MILIA, HYPOTRICHOSIS, TRICHOEPITHELIOMAS, BASAL CELL CARCINOMAS AND PERIPHERAL VASODILATION WITH CYANOSIS

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Abstract. This hitherto unknown and dominantly inherited disorder is characterized by vermiculate atrophoderma, milia, hypotrichosis, trichoepitheliomas, basal cell carcinomas and peripheral vasodilation with cyanosis. It has been present in the family reported for at least four generations. The lesions become visible in late childhood and are most pronounced on the face. Basal cell carcinomas may develop around the age of 35. Histological observations during the early stage include irregularly distributed and atrophic hair follicles, milia, dilated dermal vessels, lack of elastin or elastin in clumps. After light irradiation a tendency to increased repair activity was observed both in epidermis and in the dermal fibroblasts. On exposure to cold the change in the skin temperature of the hands compared with that in the controls was insignificant. The response to adrenalin iontophoresis was weak.

Key words: Atrophoderma; Milia; Hypotrichosis; Trichoepitheliomas; Basal cell carcinomas; Vasodilation

In this paper a hitherto unknown familial disorder of the skin is described. The syndrome has been present in the family for at least four generations and seems to have an autosomal dominant inheritance pattern. The pedigree is shown in Fig. 1. There are three main characteristic features: a facial skin with vermiculate appearance, milia-like papules, hypotrichosis and a pronounced cyanotic erythema of the lips, hands and feet. In addition, basal cell carcinomas have developed in several members of the affected family and one of them (case 2 in this report) also has numerous trichoepitheliomas. Twelve members of the family have been examined and 2 of them have been studied in detail.

CASE REPORTS

Case 1

This patient (no. VI:6 in the pedigree, Fig. 1) is a 22-year-old male forestry worker. The skin changes were first recognized at the age of 7 and have become gradually more pronounced. Hitherto, the main discomfort from this skin disorder has been cosmetic. He now has three main skin characteristics:

1. His facial skin is coarse, grainy with an almost worm-eaten appearance (Fig. 2) and a reddish-yellow tone. The vermiculate and grainy appearance is caused by a follicular atrophy with yellowish papules, often follicular, of 1–2 mm diameter, distributed all over the face. They are less apparent, however, in the areas below the nose and under the chin. Papules of the same type, although more scattered and discrete, are also found on the upper chest and back, the lateral and the extensor sides of the arms, especially around the elbows.

2. Hypotrichosis: The eyelashes are missing on the lower lids and irregularly distributed and partly missing on the upper lids; the beard is scanty, irregular and slow-growing, there are only a few scattered, thin and short hairs on the arms and the legs. Scalp hair as well as axillary and pubic hairs are soft and silky.

3. There is a pronounced, somewhat cyanotic redness of the lips, hands and feet. The lip cyanosis is most pronounced on the periphery and decreases towards the mucosal part; there is none in the mucosa. Even during winter, the hands are red and warm. The hands have a normal skin hue only when the arms are raised.

Physical examination has not revealed any other changes, and there are no dental, mucosal, cardiac, ophthalmological abnormalities.

Laboratory results. Liver function tests, serum cholesterol, triglycerides, iron, zinc, copper, were all normal. Serum electrophoresis, serum and urine lipid electrophoresis and IgG, M, D and E and retinol binding protein were normal. There was no fluorescence of the red cells. No abnormal metabolites were detected in the urine (kindly performed by L. Eldjarn, Inst. for Clin Biochem., Oslo). Radiography of the skull, lungs, heart, pulmonary vessels and aorta gave no hint of any abnormalities. Repeated electrocardiograms at rest and during physical work (150 W) were normal, as was the pulmonary function. The oxygen, carbon dioxide tensions and pH of arterial blood were normal. An EEG was normal.

Case 2

This patient (no. V:2 in the pedigree) with the most serious and advanced skin changes, is an unmarried 52-year-

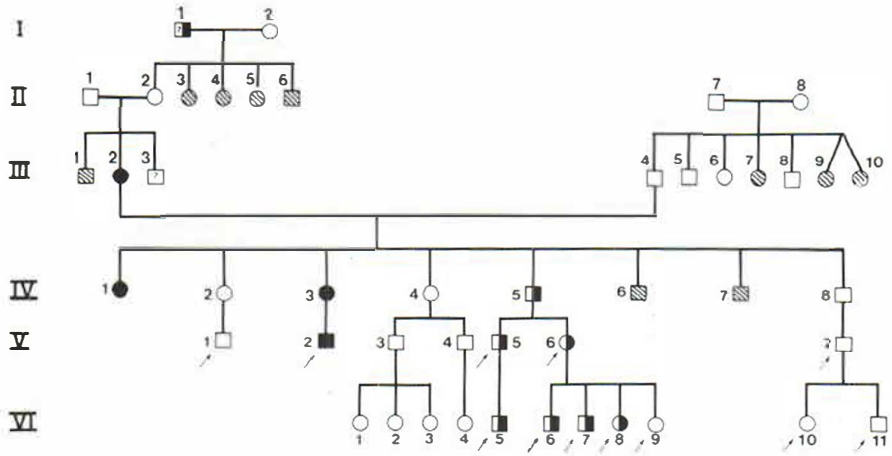


Fig. 1. Pedigree of the Rombo-Mångs family. ○ □, unaffected female and male; ○ □, syndrome without basal cell carcinoma: ○ □, syndrome with basal cell carcinoma; ○ □, died when young; ↗, personally examined.

old man with an indoor occupation. He had the same type of skin and hair changes during childhood as in case 1. In addition, since the age of 35 his facial skin has become thinner, drier, slightly scaling and at the age of 40 his first ulcerating basal cell carcinoma was diagnosed. The patient had refused to attend controls for 11 years in spite of the development of an increasing number of ulcerations and firm nodules in the facial skin. When persuaded to come for an examination, pronounced changes were present (Fig. 3) with partly atrophic, tense, erythematous, telangiectatic facial skin with a number of ulcerations overlying more infiltrated parts of the skin. The lateral part of his left nostril was completely destroyed, with free passage to the nasal cavity. In the temporal regions the skin had an orange hue with yellow-white papules of the same type as seen in case 1. About half a dozen firm, pea-sized non-ulcerated nodules were present on the cheek and forehead. The eyebrows and the beard were very sparse and the eyelashes missing. Since this patient was first seen, numerous new diffusely infiltrating lesions have developed, often with small ulcerations. The dorsal side of the hands and arms are vividly bluish-red, with plenty of telangiectatic and varicose vessels. Also on the lateral parts of the trunk numerous superficial varicose vessels are present and on the legs there are large, tortuous varicose veins. The trunk is somewhat pear-shaped, the testes of borderline size and there is a slight gynecomastia.

Laboratory results. Examinations similar to those performed in case 1 did not reveal any relevant abnormalities except for a low plasma testosterone level: 1 mg/ml. The plasma levels of luteinizing and follicle-stimulating hormone as well as urinary 17-ketosteroids and 17-hydroxysteroids were normal. There were no chromosomal abnormalities.

In addition to cases 1 and 2, 10 other members of the family were studied. Five of them had the same type of lesions as found in case 1 (Fig. 1).

Biopsies

Case 1 (and also nos. V: 5, 6 and VI: 5, 7 in the pedigree). Repeated biopsies have been taken from various skin areas: the face, neck, chest, arms, lower back and from the oral mucosa. No mucosal abnormalities have been found. All skin specimens showed the same pattern, although the changes were most pronounced in the facial skin. There was a moderate, irregular orthokeratotic hyperkeratosis and the epidermis was slightly acanthotic and irregular. The hair follicles which showed keratotic plugging were largely atrophic and very irregularly distributed. The sebaceous glands were also irregularly distributed but otherwise unaltered. The eccrine sweat glands had a normal appearance. In the dermis there were numerous milia which were thin-walled and contained a small amount of keratin and broken hairs. In the upper dermis many small vessels were dilated and sometimes surrounded by small numbers of lymphocytes. Foreign body granulomas occurred in the vicinity of the milia. One of the most striking features was the changes in the elastic fibres (Fig. 4). Elastin was entirely absent in many areas of the dermis, while others contained increased numbers of wavy, usually thin and irregular elastic fibres. Especially in the papillary dermis, distinct clumps of rather thin elastic fibres forming "steel-wool-like" balls were seen. Between these balls, the upper dermis often lacked all elastic material. The elastic laminas of the vessels were of normal appearance. Procedures employing special stains for revealing the presence of amyloid, lipids, phosphoglycerides or other abnormal substances gave negative results. Langerhans cells stained with ATPase were of normal appearance.

Case 2. In multiple punch biopsies from the facial skin, at least three different types of skin change have been found. (1) In areas with moderate changes, as in the temporal region and on the neck, the histology is similar to that in case 1. This type of change was also seen in biopsies taken from the skin of the arms and neck. (2)

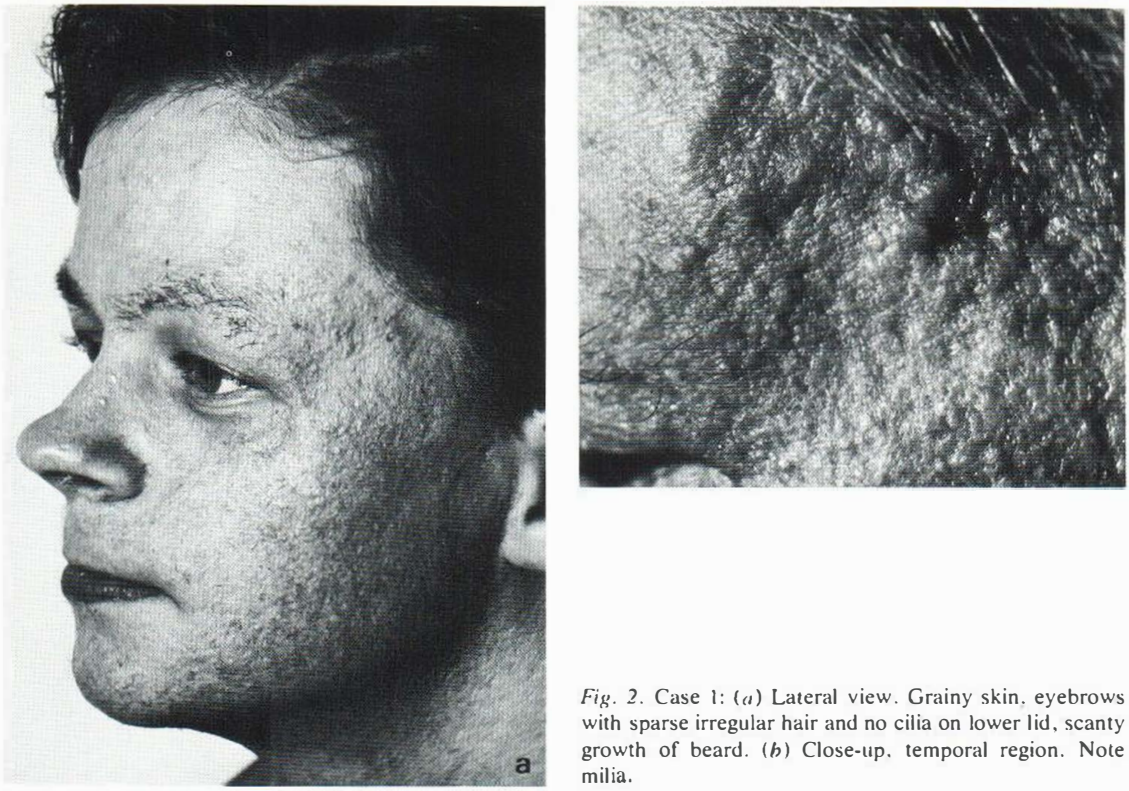


Fig. 2. Case 1: (*a*) Lateral view. Grainy skin, eyebrows with sparse irregular hair and no cilia on lower lid, scanty growth of beard. (*b*) Close-up, temporal region. Note milia.

Trichoepitheliomas were present in biopsies from six firm facial nodules. (3) Basal cell carcinomas were detected in about forty different facial biopsies. In addition the presence of all three types of change as well as an inflammation has been seen in many of the biopsies from the facial skin. Recently a squamous cell carcinoma has developed within a previously X-ray irradiated area.

Special studies

Light. Although there is no history of light intolerance, the occurrence of facial basal cell carcinomas as well as the fact that the most pronounced changes are present in light-exposed areas could imply an abnormal light sensitivity. The reactions on routine light tests (290–330, 330–380 and 400–500 nm) on the volar and lateral aspects of the lower arms and on the forehead were macroscopically similar to those in healthy controls with no signs of lowered erythema threshold.

In further studies on the reactions to light, three different areas—the volar and lateral aspects of the lower arm and the temporal part of the forehead—were irradiated at 280–330 nm (3×MED). Within each area three sites were irradiated in the same way. The same studies were undertaken in 3 healthy controls. Punch biopsies were taken before the tests, 15 min, 3 and 24 hours after the irradiation. Each biopsy was incubated with [^{3}H]-thymidine (1 μCi/ml) and processed as previously described (3). The number of densely labelled basal cells as well as the number of sparsely labelled epidermal cells per 200 epidermal cells, were counted and compared with the findings in controls. No decrease was observed in the number of densely or sparsely labelled cells. On the contrary, in the patient's specimen taken 15 min after irradiation, there were more sparsely labelled cells than in any of the irradiated control specimens. The number of sparsely labelled cells in both patients' specimens was about 90%, whereas the control values did not exceed 50–60%.

A biopsy from clinically undamaged skin on the trunk was also taken from both patients for fibroblast culture, followed by irradiation and incubation with [^{3}H]-thymidine as described by Epstein et al. (2) (kindly performed by Ass. Prof. B. Westermark). When compared with the repair activity in control specimen the patients' specimens showed increased repair activity, in the same way as in the skin irradiated in vivo.

Vascular reactions. At a room temperature of 20°C the finger skin temperature of both patients varied between 33°C and 34°C on repeated measurements on different days. After immersion of the hand in cold water (10°C) for 2 min, the skin temperature varied between 24 and 29°C, whereas in 2 controls with the same original skin temperature it was about 15°C after the cold water immersion. Oscillometry and plethysmography of the lower arms (only done in case 1) were normal.

Reactions to intradermally injected histamine, kallikrein, prostaglandin E, streptodornase/streptokinase (dos-

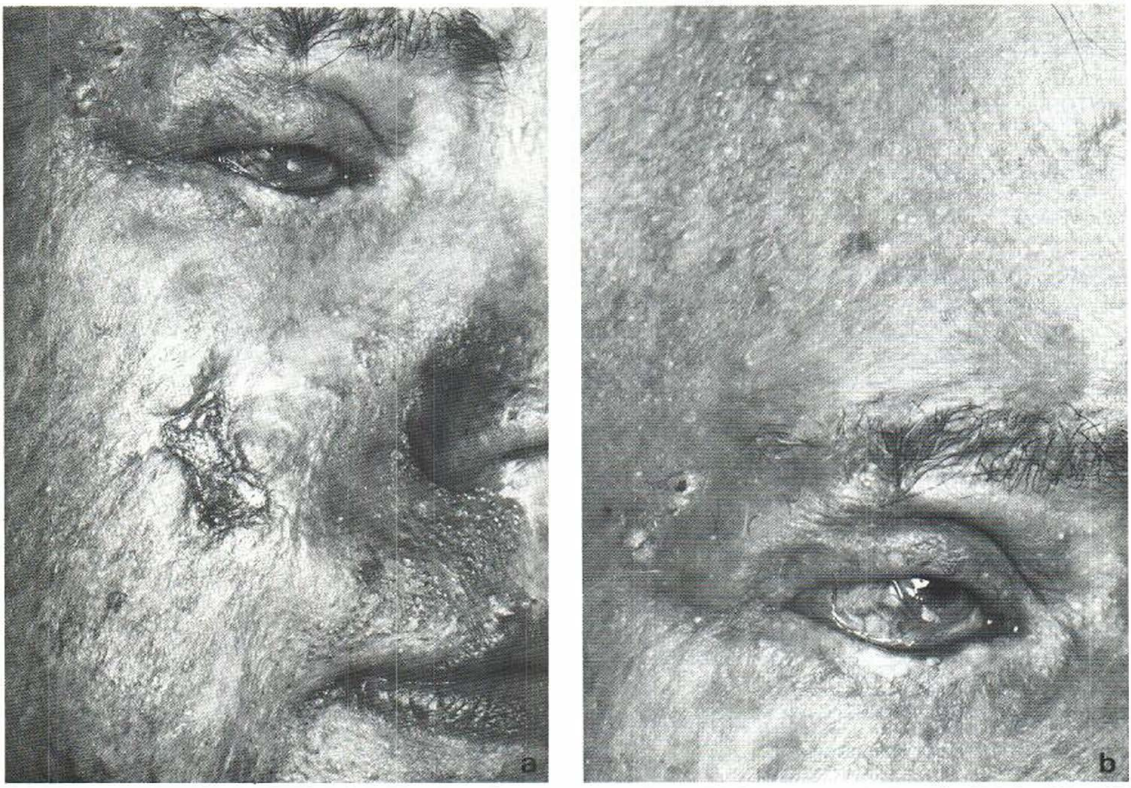


Fig. 3. Case 2: (*a*) Lateral view. Note scanty cilia, infiltrating ulcerating basal cell carcinoma on cheek, infiltrated basal cell carcinoma on upper lid. (*b*) Close-up, trichoepithelioma at lateral side of eye.

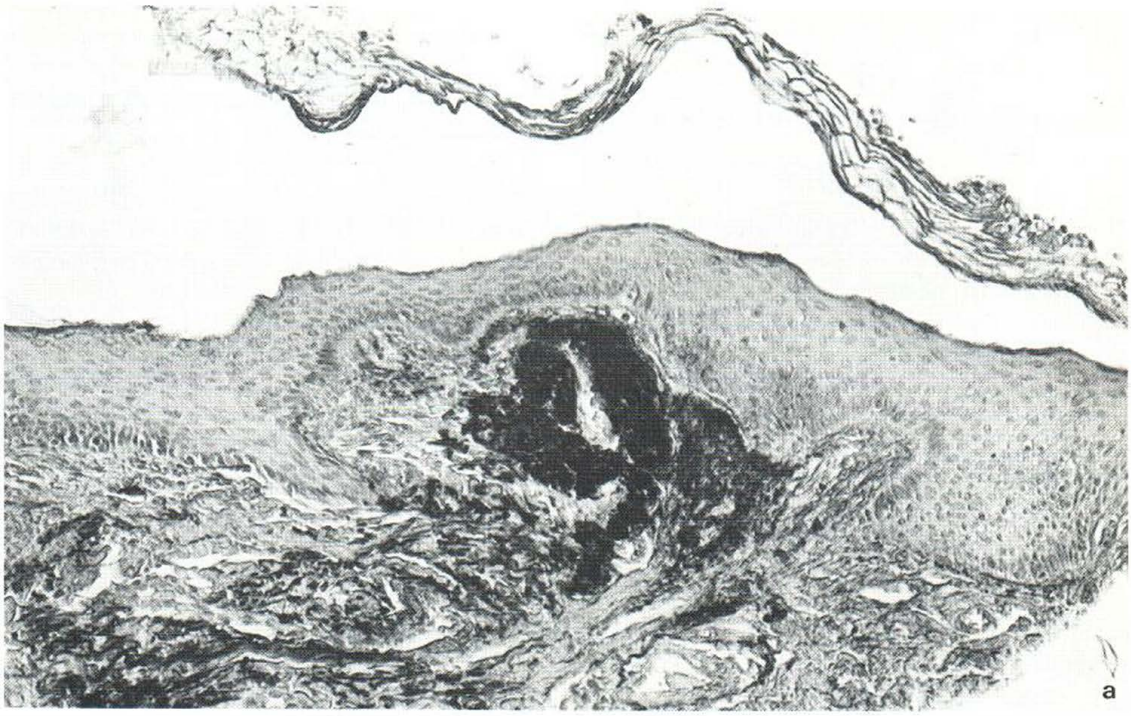
age as in ref. 4) on the volar sites of the forearm were essentially normal. Only a weak axon-reflex flare developed after histamine and kallikrein and none at all after PGE_1. However, the initial wheal induced by these compounds was unusually large.

PGE was also injected on the dorsal side of the hand. No visible erythema was observed unless the arm was raised vertical, whereas the erythema in a control subject was very pronounced. After iontophoresis with adrenalin (50 μg/ml), using the method described by Shelley & Juhlin (6) only moderate blanching was obtained. Pretreatment with a deep intradermal infiltration of 1 ml of the beta-blocker alprenolol (1 mg/ml), 10 min before adrenalin iontophoresis did not influence the degree of blanching. A number of functioning sweat glands appeared normal when stained with OPT.

Heredity. The pedigree (Fig. 1) demonstrates the autosomal dominant inheritance pattern of this syndrome in a family from the western part of Sweden. The oldest member of the family was born in 1801 and was probably affected: "looked as if he had suffered from variola". His name was Rombo. Little is known about the appearance of the skin of the other members of generations I and II. Most members of generation II (3, 4, 5, 6) died from dysenteria at an early age. In the third generation, III: 2 died at the age of 51 from facial carcinoma and II: 3 at the age of 46 of carcinoma of the neck with an unknown association with the syndrome. In generation IV, 6 of 8 children reached adult age. Three of the 6, two girls, IV: 1, 3 and one boy IV: 5, developed skin lesions. IV: 5 is the maternal grandfather of our patient no. 1 and IV: 3 is the mother of our patient no. 2. IV: 1 died at the age of 45 from widespread facial carcinoma and IV: 3 developed multiple, large and recidivating basal cell carcinomas of the face around the age of 40.

At least 4 of 7 affected family members who have reached middle age have thus developed basal cell carcinomas of the face, whereas no skin malignancies have been reported in the non-affected family members.

Fig. 4. Case 1: (*a*) The epidermis is irregular and slightly hyperkeratotic. In the dermis, accumulation of elastic material is evident, especially in the papillary parts, while other areas are almost completely devoid of elastin. Weigert's elastin, van Gieson stain, ×190. (*b*) An atrophic hair follicle is obviously in contact with one of the two milia shown in this picture. Note the irregular distribution of elastin. Weigert's elastin, van Gieson stain, ×210. (*c*) In this area the dermis is almost devoid of elastin. In the bottom, two milia are seen, one of which contains a remnant of a hair. Weigert's elastin, van Gieson stain, ×210.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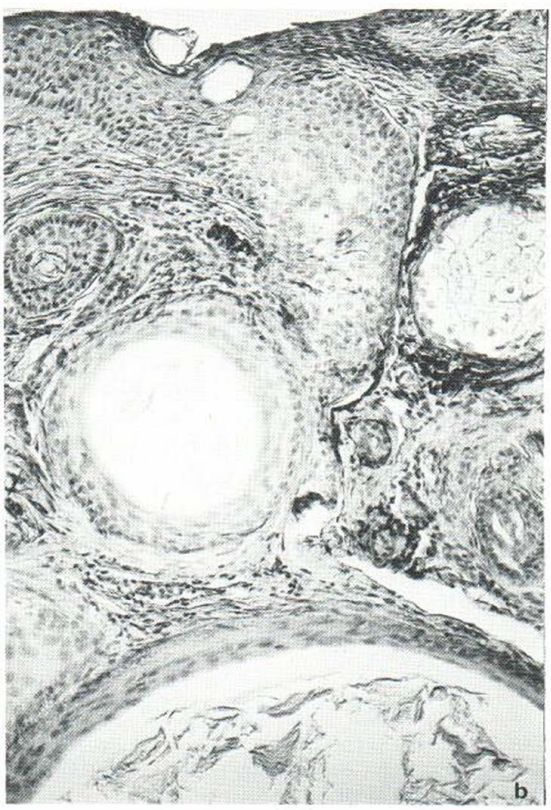
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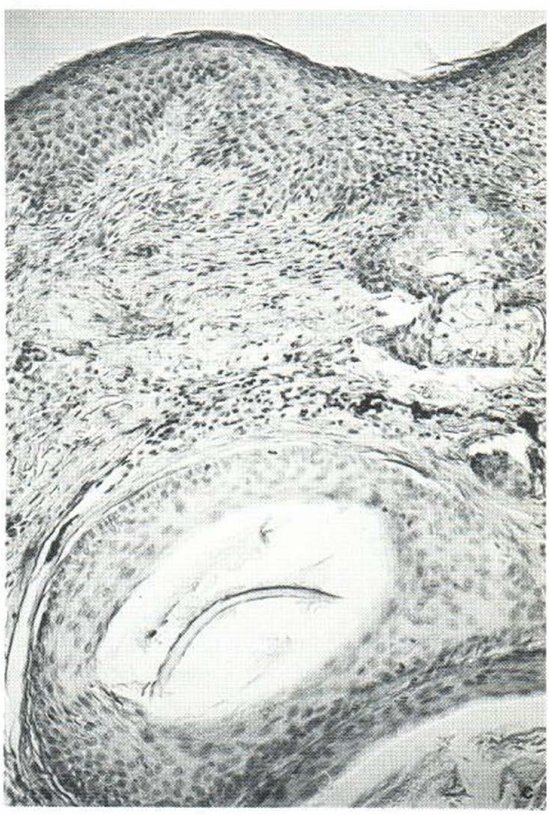
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Treatment

A dermabrasion in case 1 was followed by an improved and smoother skin. In case 2 various conventional treatments of the basal cell carcinomas have been insufficient and extensive skin grafting has recently been undertaken.

COMMENTS

We have found no description in the literature of this disorder, which we have named the Rombo syndrome after the oldest family member. It seems to have an autosomal dominant inheritance pattern. The skin changes do not appear until the age of 7–10 years. At this time the increased, somewhat cyanotic redness of the lips and hands is visible, as also is a moderate, follicular atrophy of the skin on the cheeks. Neither the yellow-whitish milia-like papules nor the telangiectatic vessels present in the adults have been observed in any of the young family members. The eyelashes and eyebrows also seem to be normal during the first years of the disorder, whereas later they are either missing or irregularly distributed, small and growing in various directions. At about the same time the yellow-whitish papules start to become visible on the cheeks and forehead. They may gradually become very conspicuous and dominate the picture. The frequency of trichoepitheliomas is not known and has been verified only in case 2. Those who do not develop basal cell carcinomas seem to suffer mainly cosmetically from the disorder.

Many clinical diagnoses have been considered, such as various types of atrophodermas, colloid milia, the basal cell carcinoma syndrome, lipoid proteinosis, amyloidosis, or some unknown type of elastosis.

The changes in the elastic fibres in the dermis were especially obvious. The increased elastic material in the dermal papillae resembles elastosis perforans serpiginosa but other features of that disorder was lacking.

The Basex syndrome (1) consisting of follicular atrophoderma, hypotrichosis and basal cell carcinomas in adolescence as well as the syndrome described by Rasmussen (5) consisting of milia, trichoepithelioma and cylindroma has some resemblance to this disorder. In the report and review of the Basex syndrome by Viksnins & Berlin (8) one of the patients also had trichoepithelioma. Our family, however, has a normal skin until later childhood and basal cell carcinomas develop later than in the Basex syndrome and are not present in all those affected. Nor is there any reduction in sweating as in the Basex syndrome. The peculiar redness of the lips and the warmth and redness of hands and feet seen in our patients have not been reported in any of the other syndromes considered.

The histological picture both in the 2 cases described here, as well as in 4 other members of the family, which is characterized by a slight or sometimes pronounced follicular hyperkeratosis and atrophic hair follicles sometimes surrounded by inflammatory changes, milia-like bodies and patchy elastosis, and ectatic vessels surrounded by minor lymphocytic infiltrations, gives no information as to the primary site of the lesions. The increased redness and the higher skin temperature after exposure to cold compared with that in the controls, and the insignificant response to adrenalin as well as large oedematous reactions to histamine and kallikrein, may well indicate that changes in the blood vessels play an important role, although no specific vascular changes have yet been demonstrated. The vascular component in this disorder is very marked in patient 2, who has much more severe symptoms, with erythema and angiectasies not only on light-exposed areas but also on the trunk and the extremities. This patient also has numerous trichoepitheliomas and it might be speculated that these tumours represent the next stage in the development of the changes observed in the milder cases. Hence Thies & Schwarz (7) have suggested that milia might be a form of trichoepithelioma.

The most pronounced changes, including the tendency to develop basal cell carcinomas, appear in light-exposed areas. This would suggest abnormal reactions to light. However, macroscopically the reactions have been normal after light exposure. Autoradiography has not revealed any of the characteristics of xeroderma pigmentosum or of pigmented xerodermoid. The results of autoradiographic studies, however, have indicated an increase in repair activity in all biopsies, taken 15 min after exposure to light, from both patients when compared with biopsies from controls. The same results were obtained after irradiation of fibroblast cultures. The relevance of these findings is as yet obscure.

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