

## Cowden's Disease in Three Siblings: Electron-microscope and Immunological Studies

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Cowden's disease was diagnosed in three siblings (two sisters and a brother) in a Jewish Israeli family of Yemenite origin. The typical mucocutaneous lesions of the disease were present in all three cases. There were hamartomas involving other body systems, including euthyroid multinodular goiter (in all 3 cases), gastrointestinal polyposis (in 2 cases) and hemangioma (in one case). Developmental anomalies were found in all 3 cases. Histological examination of mucocutaneous lesions was in accordance with previous descriptions, including the findings compatible with trichilemmoma observed in cutaneous facial papules. Extensive electron-microscope studies of these facial lesions yielded no evidence of viral particles. Immunological studies, carried out mainly in two cases, revealed a decrease in complement level in the serum and impairment of T cell function. *Key words: Hamartomas; Multinodular goiter; Gastrointestinal polyposis; Trichilemmoma.* (Received August 21, 1984.)

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Cowden's disease (multiple hamartoma syndrome), originally reported in 1963 by Lloyd & Dennis (1), is a rare genodermatosis inherited as an autosomal dominant trait with a one to one sex ratio (2).

We describe three siblings (two sisters and a brother) of a Jewish Israeli family of Yemenite origin who have Cowden's disease. Also presented are the findings of light-microscopic and electron-microscopic studies of various lesions as well as the results of immunological studies, carried out mainly in two of the cases.

### CASE REPORTS

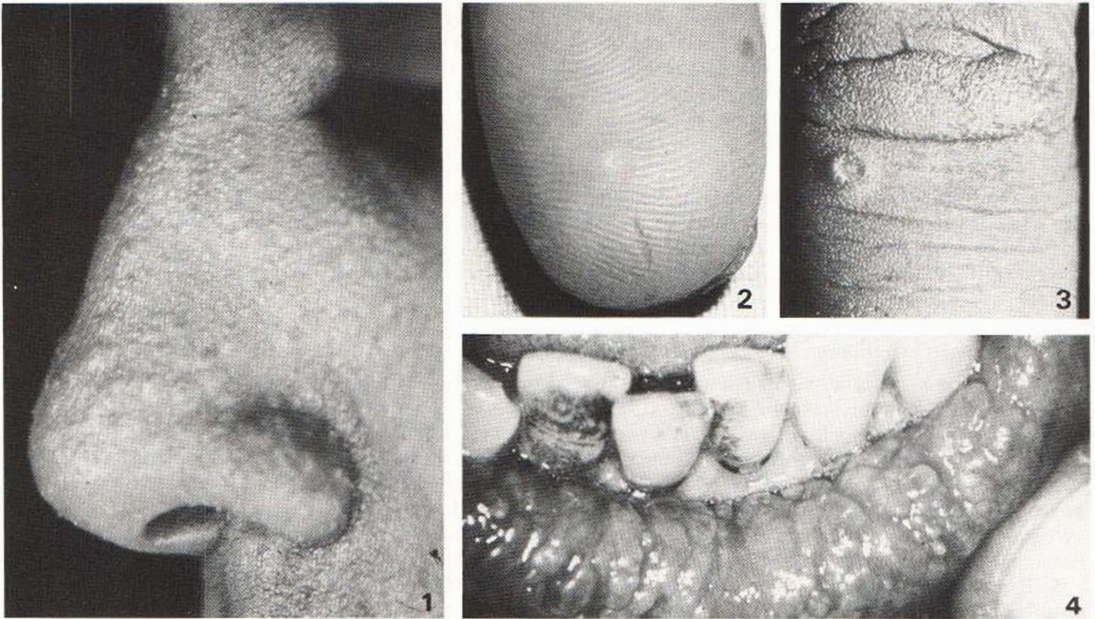
#### *Case 1*

A 19-year-old woman was seen in our out-patient clinic in July 1984 because of progressive disfiguring changes on the lips and face. The medical history revealed that she had had a thyroid goiter since childhood as well as menstrual irregularities. The physical examination disclosed mild mental retardation, thyroid goiter, adenoid facies and prominent mucocutaneous lesions of the oral mucosa, face, hands and feet.

The oral lesions consisted of marked hypertrophy of the lips and oral mucosal papillomatosis. There were multiple pink-red papillomatous lesions one to several millimeters in diameter on the lips, in the mouth angles and on the buccal mucosa, gingiva, palate, oropharynx and tongue. These lesions showed a tendency to coalesce, giving the affected mucosal surface a "cobblestone appearance". Other oral findings included a scrotal tongue, high-arched palate, marked caries of the teeth and spots of hyperpigmentation on the buccal mucosa.

The facial lesions consisted of numerous flesh-colored flat papules a few millimeters in diameter located especially on the central aspect of the face (Fig. 1), but also on the forehead, retroauricular region and sides of the neck.

The acral lesions included a number of skin-colored verrucous hyperkeratotic papules 1-4 mm in diameter, some with a central umbilication, located on the dorsa of hands and feet. These lesions, which were diagnosed clinically as acral keratoses, resemble the lesions of viral warts or acrokerato-



*Fig. 1.* Flesh-colored cutaneous facial papules on central aspects of the face (case 1).

*Fig. 2.* A punctate translucent keratosis on the palmar aspect of a finger (case 1).

*Fig. 3.* An acral keratosis with a central umbilication on the dorsal aspect of a finger (case 2).

*Fig. 4.* Papillomatosis of the lips with marked caries of the teeth (case 3).

sis verruciformis (Hopf). Additional acral lesions consisted of a few hard punctate translucent shiny papules 1–2 mm in diameter with a central dell, which were located on the palmar aspect of the fingers, interfering with the normal skin lines (Fig. 2). These lesions were diagnosed clinically as palmar keratoses. Also noted on the palms were linear bands of hyperpigmentation. The rest of the physical examination, including a gynecological examination was unremarkable.

#### Case 2

In 1976 the 23-year-old brother of Case 1 appeared in our out-patient clinic. He was mentally retarded with psychopathic behaviour and was found to have a thyroid goiter from the age of 10 years. The physical examination revealed adenoid facies and mucocutaneous lesions almost identical to those of his sister consisting of oral mucosal papillomatosis, flesh-colored facial papules, acral keratoses on the dorsa of hands and feet (Fig. 3), punctate translucent palmar keratoses and round spots and bands of hyperpigmentation of the palms. Other findings included a scrotal tongue, high-arched palate, hemangioma near the right tonsil, a large soft thyroid goiter and lymph node enlargement in the inguinal regions as well as the left axilla. The rest of the physical examination was without pathological findings.

In February 1980, he underwent removal of the right lobe of the thyroid gland in another hospital because of marked difficulties in breathing and swallowing, the histological findings being consistent with multinodular adenomatous goiter. Ten months later, in December 1980, he developed ileo-cecal intussusception due to polyposis of the terminal ileum. Histologic examination of a polyp excised from the terminal ileum revealed hamartoma angiolipomatosis.

#### Case 3

In 1981 the 28-year-old sister of the above also appeared in our clinic. She was known to have had a multinodular goiter since childhood and in October 1979 had undergone sub-total thyroidectomy, the histological finding being nodular goiter. Also of note in the patient's medical record were menstrual irregularities and epigastric hunger pains.

The physical examination revealed mild mental retardation, thyroid goiter, adenoid facies and

mucocutaneous lesions similar to those observed in her siblings. These included oral mucosal papillomatosis (Fig. 4), flesh-colored and grey lichenoid facial papules, keratoses on the dorsa of the feet and punctate translucent palmar and plantar keratoses. Also found were a scrotal tongue, high-arched palate and spots of hyperpigmentation on the buccal mucosa. The rest of the examination, including a gynecological examination, was normal.

#### *Family history*

The parents of these three siblings were of Yemenite origin and non-related. The mother died at the age of 30 due to giant follicular carcinoma of the thyroid with generalized spread but no information could be obtained regarding the presence of mucocutaneous lesions or other systemic abnormalities. Another two siblings (a younger sister and brother) had only a few facial papules which had gone unnoticed, without any other known abnormalities.

#### *Histological and electron-microscope studies of mucocutaneous lesions*

1. Examination of a facial papule from case 1 revealed proliferation of follicular sheath epithelium extending into the dermis, resembling a distorted hair follicle. At the periphery of the hair follicle the cells were arranged in a palisade resting on a prominent basal membrane (Fig. 5). These findings are compatible with the diagnosis of trichilemmoma. A facial papule from case 3 showed similar findings.

2. Examination of a facial papule from case 2 revealed a lobulated tumor connected to the epidermis, containing groups of large epithelial cells with small round nuclei and abundant pale cytoplasm (Fig. 6). The peripheral cells of the tumor were arranged in a palisade lying on a thickened basal membrane (Fig. 7). These findings are compatible with the diagnosis of a trichilemmoma.

3. Examination of an oral lesion from case 3 revealed a fibrovascular core surrounded by hyperplastic epithelium with slight hyper-parakeratosis (Fig. 8). The rete ridges were thickened and elongated and showed connections between them.

4. Examination of acral verrucous papules from cases 1 and 2 revealed marked hyperkeratosis, acanthosis and papillomatosis, suggesting the histological findings of acrokeratosis verruciformis (Hopf).

Electron-microscope examination of a facial papule obtained from case 2 showed two types of cells, one showing dark cytoplasm with abundant tonofilaments arranged in groups or whorls and abundant glycogen granules arranged in clusters (Figs. 9, 10) and the other with pale cytoplasm, few organelles and no tonofilaments, with glycogen granules dispersed in the cytoplasm (Fig. 9). Both types of cells were connected with desmosomes but in the clear cells there were no bundles of tonofilaments adhering to the desmosomes (Fig. 9). An extensive search for virus particles was negative.

#### *Laboratory investigations*

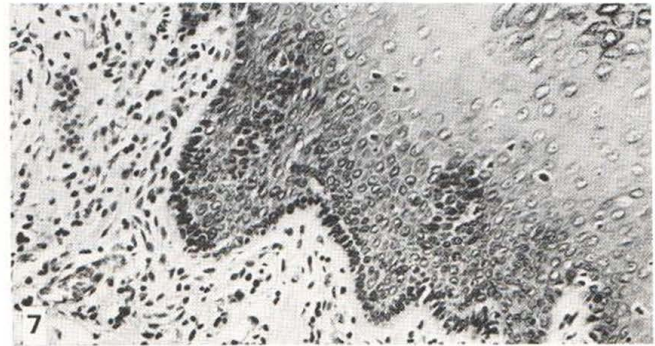
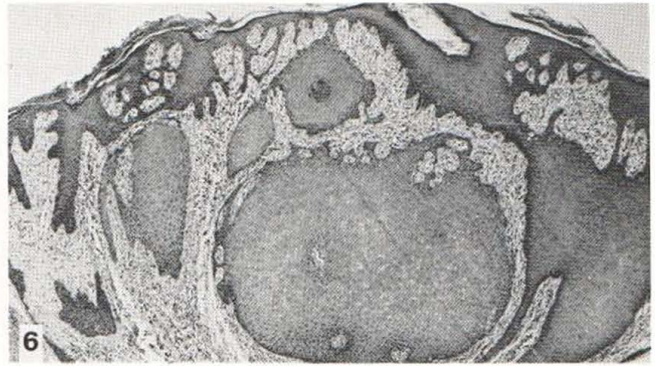
In the search for an underlying malignancy or other anomalies numerous laboratory and X-ray examinations were carried out in all three siblings.

Thyroid scanning revealed non-homogeneous multinodular goiter, with a lower uptake in the left lobe than in the right (case 1); homogeneous multinodular goiter (case 2); and a "cold nodule" in the region of the thyroid isthmus (case 3). Other pathological findings consisted of the following: a deformation of the bulbus duodeni due to ulcer (cases 1 and 3); numerous polyps of the rectosigmoid without evidence for malignancy (case 1); diffuse enlargement of the liver, without evidence of a space-occupying lesion (case 3); slight atrophy of the alveolar process of the maxilla (case 2); and a positive Australian antigen (case 2).

#### *Immunological studies*

Immunological studies were carried out mainly in cases 1 and 3, and these consisted of the following: electrophoresis and immuno-electrophoresis of serum proteins; complement levels in the serum ( $C_3$ ,  $C_4$ ,  $C_{H50}$ ), percentage of macrophages, B and T lymphocytes in peripheral blood, skin tests for delayed hypersensitivity, blastic response of peripheral lymphocytes towards the mitogens phytohemagglutinin and pokeweed mitogen, the functional capacity of T lymphocytes measured by the graft-versus-host reaction (GVHR) (3), suppressor cell level and histocompatibility antigens.

The pathological findings consisted of the following. In case 1 the level of  $C_3$  in serum was decreased to 54 mg% (normal range  $125 \pm 25$  mg%) and the hemolytic complement decreased to 40% (normal range 50–100%); the blastic response of T lymphocytes towards phytohemagglutinin was markedly reduced, the maximal response obtained in a dose-response curve being 5080 cpm whereas a value of 15000 cpm is considered to be normal. In case 3 the level of  $C_3$  in serum was decreased to 75 mg% and there was an impairment in the functional capacity of the T lymphocytes, as measured by the graft-versus-host reaction.



*Fig. 5.* Trichilemmoma showing a distorted elongated and widened hair follicle (case 1). (H & E,  $\times 35$ ).

*Fig. 6.* A lobulated tumor with palisading of basal cells and groups of clear cells (case 2). (H & E,  $\times 35$ ).

*Fig. 7.* High magnification of Fig. 6, showing thickened basal membrane and palisading of the basal layer (H & E,  $\times 200$ ).

*Fig. 8.* Oral lesion showing fibrovascular core surrounded by hyperplastic epithelium (case 3). (H & E,  $\times 35$ ).

All 3 siblings showed identical histocompatibility antigens, consisting of \*3, AW33, B14, B18 and CW8.

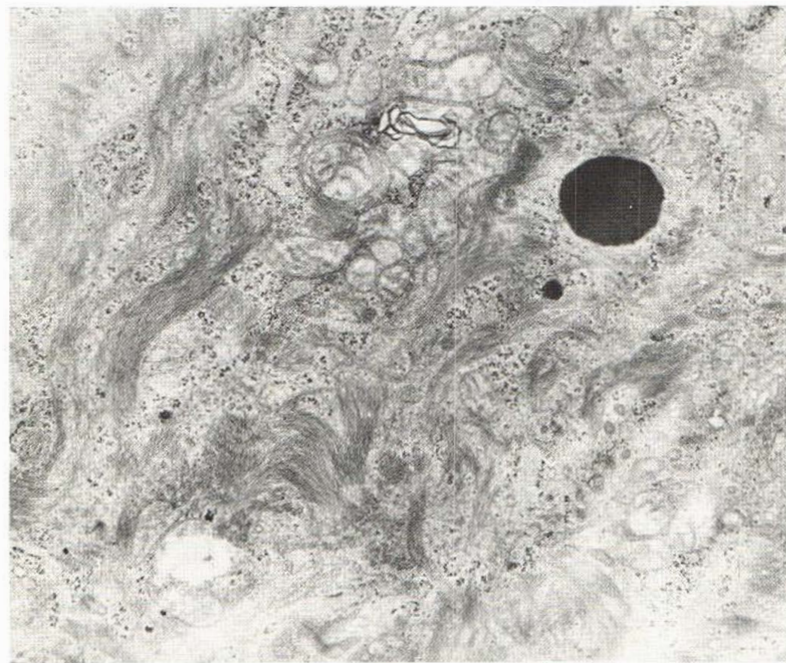
## DISCUSSION

Since the original report of Lloyd & Dennis (1) in 1963, 46 cases of Cowden's disease have been reported in the literature (2). In the three siblings presented here it was possible to make a definite diagnosis of Cowden's disease based on the presence of the criteria proposed by Salem & Steck (2). However, only a probable diagnosis of Cowden's disease, or "forme fruste" of the total syndrome complex, is suggested in the two youngest siblings in this family (4).



*Fig. 9.* EM examination of tumor seen in Figs. 6 and 7, showing two cell types: dark cells with clusters of glycogen granules and clear cells with glycogen dispersed in the cytoplasm ( $\times 8\ 400$ ).

The histopathological findings in the various mucocutaneous lesions of the three siblings are similar to those reported by Brownstein et al. (5) and include the trichilemmomas on the face, the findings observed in the oral mucosal lesions and those suggestive of acrokeratosis verruciformis (Hopf) in the acral keratoses. As in our cases, these authors did not find any viral particles in the electron-microscope studies of facial trichilemmomas.



*Fig. 10.* EM examination, showing bundles of tonofilaments arranged in irregular fashion. Within the cytoplasm there are concentric forms of endoplasmic reticulum ( $\times 10\ 000$ ).

In the search for other possible etiological factors in Cowden's disease, Ruschak et al. (6) recently carried out an immunological study in a single patient, finding an underlying defect in T cell function but unaltered humoral immunity. The findings in our immunological studies, carried out mainly in cases 1 and 3, were not consistent, with abnormalities involving both humoral and cellular immunity. These included a decreased level of complement in cases 1 and 3 as well as an impairment in T cell function in both.

Malignancy was found in 45.6% of the 46 reported patients with Cowden's disease with carcinoma of the breast being by far the most frequently reported malignancy, and cancer of the thyroid being next in order of occurrence (2). Although no malignancy has yet been found in our three cases, the "cold nodule" found in case 3 may indicate a developing thyroid cancer, the same type of malignancy from which her mother died.

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