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INCONTINENTIA PIGMENTI WITH ASSOCIATED LESIONS IN TWO GENERATIONS

Clinical, Light Microscopic, and Electronmicroscopic Examinations

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Abstract. Four cases of incontinentia pigmenti are reported, viz. a mother and her three daughters. Case history of the mother described bullous skin eruptions during infancy; at present minor reticular pigmentations and areate alopecias are present.

She has had five pregnancies, and has given birth to three daughters who all exhibited bullous skin eruptions soon after delivery. Two of her pregnancies terminated with male abortions, both occurring during the 20th week. One of the daughters, $2\,^1/_2$ years old, developed leukemia for which she was treated with steroids and cytotoxic drugs. The youngest daughter (our proposita) presented with a pseudoglioma of the left eye at the age of 15 months. Light microscopical examination of the skin was done in the mother, and both light microscopic and electron microscopic examinations in one of the children. At electron microscopy, a hyperkeratotic epidermis of normal structure was seen, containing numerous melanin granules intracellularly in the basal layer. The granules were arranged in clusters and in some instances surrounded by monolayer membranes.

About 300 cases of incontinentia pigmenti (i.p.) are found in the literature to date. Garrod (6) reported a $2\,^1/_2$-year-old girl who had skin lesions similar to those later referred to as i.p. Bardach (3) demonstrated monozygotic twins who presented with pigmentations diagnosed as systemic naevus. The 4th case, reported by Bloch (5) was later described by Sulzberger (13) as incontinentia pigmenti, hence known as Bloch-Sulzbergers disease.

In 1953 Asboe-Hansen (1) wrote of pigmented and keratogenous dermatitis with eosinophilia in newborn girls, and in 1966 (2) claimed this disease to be a prodroma of i.p.

I.p. is familial but the mode of inheritance is unknown. Thus different hypotheses have been proposed concerning the aetiology. Lenz (8) supposed that the syndrome was inherited via an X-linked dominant gene, being lethal in boys, and in support of this hypothesis, it may be demonstrated that the disease is transmitted by affected women who have a rather low incidence of male children in their offspring.

Pfeiffer (11) submitted the hypothesis that the disease, caused by an autosomal dominant gene, was sex-limited in its manifestation, thus explaining why it occurs predominantly in females. Other theories of inheritance have been postulated, e.g. that it was caused by a cytoplasmic factor lethal in males, earlier cytoplasmic inclusion bodies like those demonstrated in molluscum contagiosum having been demonstrated by Murrell (10). Furthermore, since the early phase of the disease resembles an inflammatory reaction due to the occurrence of numerous eosinophils in the skin, liver and spleen, Küster & Olbing (7) hypothesised that an infection was the etiological factor.

I.p. is very often associated with other ectodermal and mesodermal defects, among these being bone deformities, congenital heart diseases, urachus cysts and supernumary lobules of the ear.

Eye complications in connection with i.p. have been described extensively by Wollensak (15) and by Benedikt & Ehalt (4). Anomalies of the eye have been observed in 25 % of patients. Among these are corneal opacities, congenital cataract, malformations of the iris, persistent hyperplastic vitreous and prenatal and postnatal uveitis or chorio-retinitis. Furthermore, optic atrophy,

microphthalmos, hydrophthalmos, squint and nystagmus also have been described.

Often the above-mentioned retro-lenticular changes resemble a tumour of the eye, especially retinoblastoma, and several eyes were enucleated on this suspicion. It should be pointed out, however, that signs of malignancy, e.g. extraocular growth or spread have never been described, and histological examination has never verified retinoblastoma (4).

The histological picture of i.p. is non-specific. So-called pigmentary incontinence has been registered in other diseases, e.g. lupus erythematosus, poikiloderma vasculare atrophicans, lichen planus, melanodermatitis toxica and erythrodermia (9). The histological picture has been described as autochton tattooing due to the predominantly intracellular occurrence of melanin pigment, in the upper part of the corium.

Recently the ultrastructural changes occurring in the pigmented papule stage of i.p. were described in a newborn girl by Wong et al. (16). The present report concerns a family presenting with i.p. in at least two generations, in the younger of which several complications were registered. Furthermore it seems to be the first report of electron-microscopic examinations of the later stages of i.p.

MATERIAL

A. *Case Reports*

1. The mother, who is now 36 years old, had during her first 9 months of life vesicles on her skin which were treated with different ointments by a dermatologist, supposing it to be a neonatal pemphigus. Vestiges of brownish pigmentations are still visible on her left breast and in her left axilla. In her scalp small areas of alopecia are present, though associated pigmentation has not been demonstrated. A biopsy taken from the axilla has shown a band of melanin-containing macrophages in the upper part of the corium. She had 5 pregnancies, 2 of which were miscarriages, causing male abortions in the 20th week. The other three pregnancies resulted in girls.

2. The eldest girl was born in 1962 one month before term after a non-complicated pregnancy. At birth the child exhibited vesicles in the groin, which were treated with incision and mercury ointment. As a sibling she is said to have been rather restless with vomiting and abdominal pains, though the pediatricians were unable to demonstrate any abnormality. At 2 months she developed brownish streaks on both legs, extending over the abdominal wall, later spreading to the whole trunk, terminating in the ear, but besides this there were other pigmentations on her face. At the age of 5 most of these pigmentations had disappeared and at the present time only faint reticular pigmentations are present in the groins.

3. The second girl was born in 1966 after a normal pregnancy. At birth a few vesicles were present on the right thumb. At 2 months brownish pigmentations on the right knee were observed, and later also on the abdomen, in the groin and on the upper extremities. At $2\frac{1}{2}$ years she was transferred to a medical department because during the previous 2 months she had complained of fatigue and pains and at the same time had shown increasing pallor. Furthermore, she complained of bone pain, most pronounced in hand and feet, but no bleeding from the skin or mucous membranes was observed. The temperature was between 37° and 39°C, and on admittance she was found to have a haemoglobin value of 38% and white blood cell count of 4 000 with a 100% lymphocytes or stem cells.

On admission there was slight lymphadenopathy and a brownish reticular pigmentation, described in the record as resembling old dirt. During the first days in hospital the white blood cell count fell to 1 200, and the blood platelets to 33 000. Marrow smear was not taken. A few days later steroid treatment was initiated, and blood transfusion given, though no remission was seen until the treatment was supplemented with puri-nethol (mercapto purin) 25 mg daily.

The child was dismissed in a fair condition after $1\frac{1}{2}$ months in the medical ward, and since her stay in hospital 3 years ago, the treatment has been continued. The latest blood test (1971) has shown: white blood cell count: 6 000, with normal distribution and 1% eosinophils.

X-ray of her legs showed on both thighs just over the epiphyses a little metaphyseal clear spot with a sclerosing zone in the vicinity of the epiphyses, the limit at the other end being less distinct. The change in the bone was probably localized. The cortex was intact, and there was no periostal callus reaction. In the distal part of the tibia similar though less prominent changes were observed. The present change has been described as the most common abnormal X-ray finding in childhood leukemia (14).

4. The 3rd child was born in June 1969. At birth she had vesicles which soon disappeared, leaving pigmentations which are still present. At birth there were also vesicles in the scalp which have since disappeared, leaving pigmented areas of alopecia.

The mother, who is very well aware of the clinical signs and symptoms, has informed us that the primary changes consisted of vesicles on the extremities and in the groins with pigmentation of the trunk.

When the patient was 15 months old her mother observed a yellow opacity in the pupil of the left eye. After examination by the local ophthalmologist the girl was admitted to the eye department on the suspicion of tumour in the eye. There was a left convergent squint of 10°. In the anterior chamber there was evidence of previous uveitis, i.e. posterior synecchia to the otherwise normal lens. The cornea, tension and dimensions of the eye were normal. Ophthalmoscopy revealed funnel-shaped

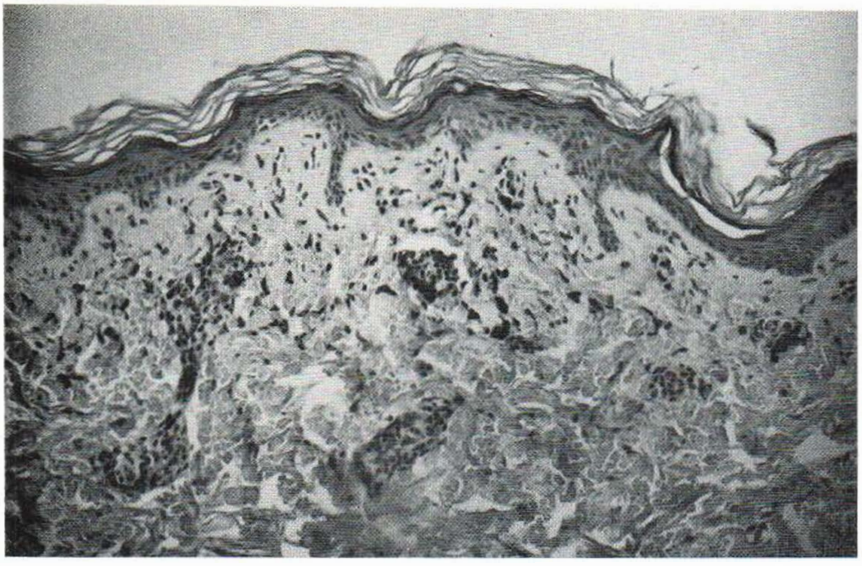

Fig. 1. Case 4. Biopsy showing hyperkeratosis without significant changes in the epidermis. In the upper part of the corium is a diffuse accumulation of melanophores and some inflammatory and connective tissue cells (lymphocytes, plasma cells, mast cells and histiocytes). The deeper part of the corium is of fibrous appearance. H & E, × 140.

grey membranes, resembling retinal ablation, with a more compact mass of tissue behind. Just posterior to the lens there was a fine, translucent membrane with vessels. No elongated ciliary processes were present. The right eye was normal. Sero-reactions for toxoplasmosis were negative. The conclusion after repeated examinations was that the eye represented a typical picture of a pseudo-glioma, and it was decided to omit enucleation but to keep the patient under observation. Consequently, it is not possible to present histological examination of the eye.

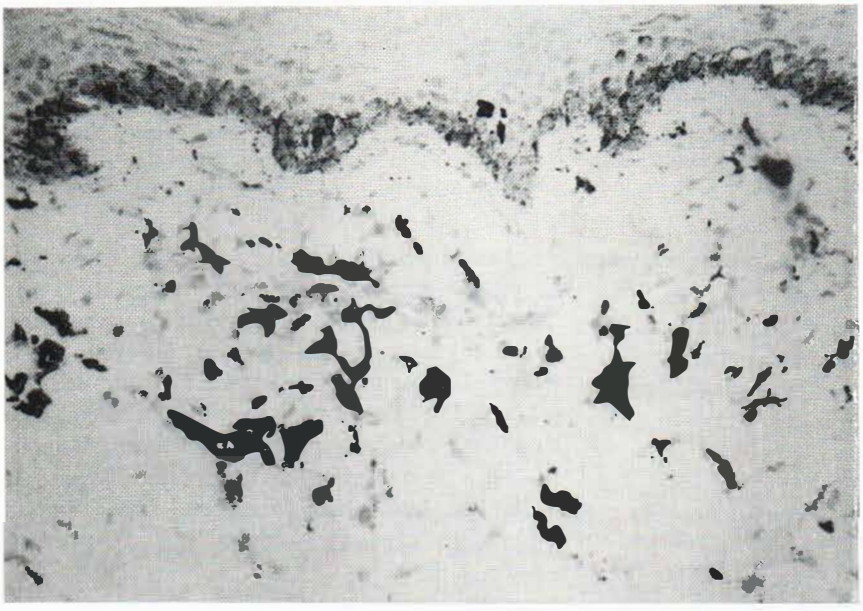

Fig. 2. As Fig. 1 at higher magnification and stained with Fontana-Masson ammoniacal silver method for melanin. A rather pronounced melanin content is seen in the basal part of epidermis with some extension to stratum spinosum. In the corium a band of large melanophores is found. Fontana-Masson, × 350.

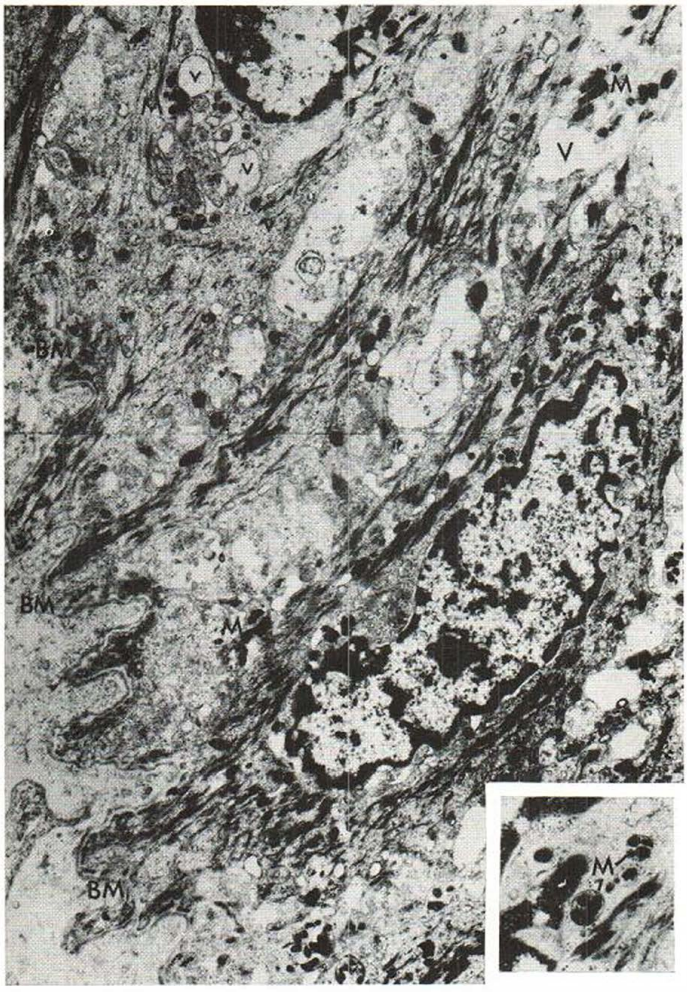

Fig. 3. Electronmicrograph of dermo-epidermal junction with the basement membrane (BM) running tortuous and uninterrupted to the left. Melanin granules (M) are found scattered at random in the cells, sometimes close to vacuoles (V) in the cytoplasm. *Inset* shows compound melanin granules. × ca. 8 150; inset × ca. 16 300.

B. *Histopathological and Electron-microscopical Investigations*

Skin biopsies were obtained from the youngest child (case 4) and from the mother (case 1). From the child two biopsies were available, one of which was used for electron-microscopy.

I. *Light microscopy (cases 1 and 4)*

The biopsies were fixed in 4% basic lead-acetate and in buffered formalin. The following staining technique was used: Watery toluidine blue (0.1%) on lead-acetate fixed tissue in order to demonstrate metachromasia and mast cells. On formalin-fixed tissue the following staining techniques were used: hematoxylin-eosin, van Gieson, Fontana-Masson, Alcian Blue a.m. Mowry, Weigert's elastin method.

Results. Both mother and child showed an identical histology, i.e. there was severe hyperkeratosis but normal differentiated squamous surface epithelium, which showed, however, an increased pigmentation in the basal cell layer (Figs. 1 and 2). The dermis showed fibrosis and at a certain distance from the epithelium a band of heavily pigmented melanophores was present. In toluidine blue stained sections, metachromatic granulated mast cells occurred in juxtaposition to some of these.

II. *Electron-microscopy (case 4)*

The tissue was fixed immediately in 6% glutaraldehyde for 24 hours and then placed in sucrose buffer, pH 7.2.

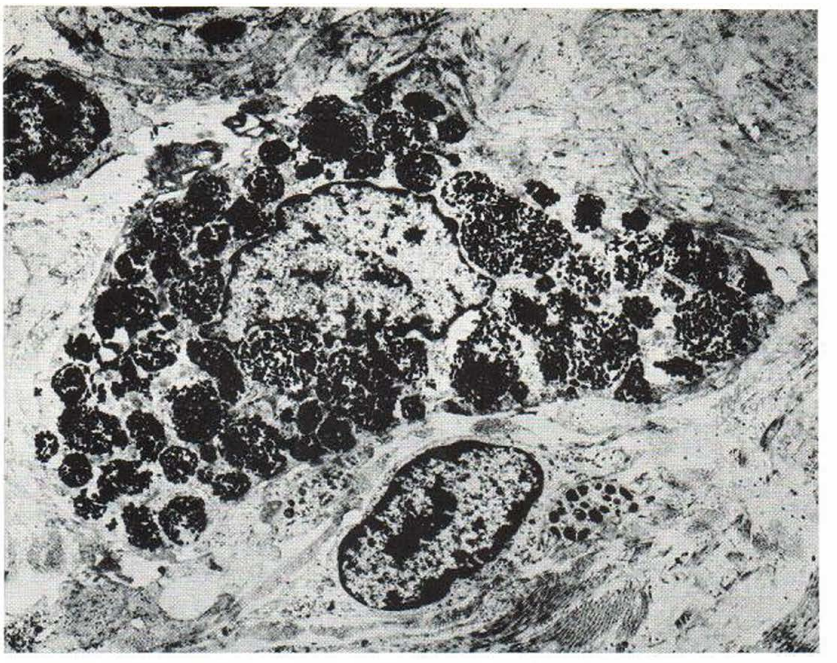

Fig. 4. Electronmicrograph of melanophore with large accumulations of aggregated melanosomes and surrounded by bundles of collagen fibrils and other connective tissue cells. × ca. 4 500.

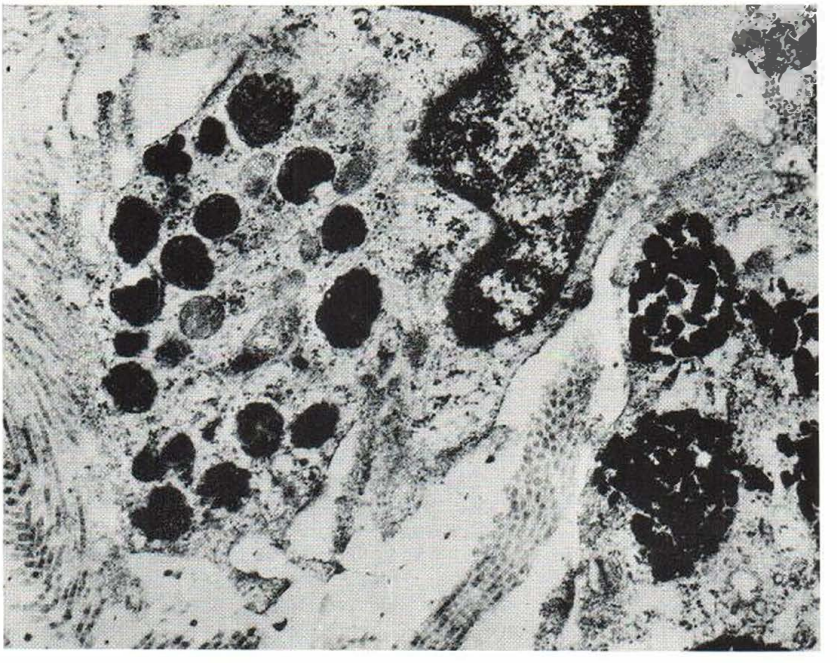

Fig. 5. Electronmicrograph showing mast cell with typical granules in juxtaposition to portion of melanophore (right). × ca. 20 000.

After dehydration it was embedded in Epon. Semifine sections were cut 1 μm thick for orientation purposes, and ultrafine sections cut on an LKB II ultramicrotome. After-staining was done with uranyl acetate and lead hydroxide. The investigations were done by use of JEM T7 and Hitachi HS-8 electronmicroscopes.

Results. Other than hyperkeratosis, the epidermis showed normal structure. In the basal cell layer numerous melanin granules were found intracellularly. These granules were often arranged in clusters, some of which obviously enclosed by mono-layer membranes (Fig. 3).

In the melanocytes were small and empty vacuoles, now and then in close relation to melanin granules. However, similar but larger

vacuoles were also present in other cells of the basal layers. The basement membrane was seen to be tortuous and of normal thickness and structure but no gaps were observed. No definite pathological changes were observed in the dense collagenous tissue or in the elastic membranes.

The melanophores had a nucleus of rather common lobulated appearance and an ordinary chromatin distribution. The cytoplasm was filled with groups of melanin granules packed close together (Fig. 4). The mast cells seen in light microscopy were of normal appearance and did not contain melanin granules (Fig. 5). The dermis did not contain extracellular melanin granules.

DISCUSSION

The family published comprises two generations, a mother and her three daughters, all suffering from incontinentia pigmenti (i.p.). A striking feature in our material is that the mother's five pregnancies resulted in the birth of three girls all of whom suffered from a bullous eruption, later on developing into typical i.p., and that her two other pregnancies terminated in male abortions, both occurring in the 20th week. Shotts & Emery (12) reported a case where a woman had an eye enucleated due to a lenticular opacity—one of the ophthalmologic complications inherent in i.p. The two first pregnancies of this patient terminated in abortions in the 5th month, the first being a male abortion whereas the sex in the second case was not recorded in her files. However, both abortions occurred at the same stage of pregnancy as in our patient, thus supporting the hypothesis that i.p. is lethal in males, at least in some instances.

It is regrettable that no dermatologist with knowledge of i.p. saw the children in our material during their infancy but, anamnestically, both the mother and her three girls exhibited bullous and papular eruptions soon after birth. This must be taken as support of the bullous and papular phase being the prodrome of i.p.

The second daughter, case 3, developed at 28 months of age a condition interpreted in a medical ward as acute leukemia. Steroid treatment did not achieve remission which first occurred when steroids were supplemented with a cytotoxic drug. It is not possible in her case to correlate the i.p. to her possible leukemia. However, a pure coincidence of these two rare diseases might be regarded as utterly remote.

Benedikt & Ehalt (4) elicited, from various materials in the literature, that eye complications occur in 25 to 30% of patients with i.p. One out of our four patients showed eye complications of a kind previously described in connection with i.p.

The findings of Wong et al. (16) of vacuolization of the cytoplasm of melanocytes were, albeit to a lesser extent, observed in one of our patients, although no myelin figures were observed in our case. Gaps in the basement membrane and release of melanin granules or dendritic processes of melanocytes which penetrated down into the upper part of dermis containing melanin granules (as observed by Wong et al.) was not confirmed in our material. This discrepancy between the two materials may be caused by the examination of Wong et al. of the pigmented papule stage whereas our electron-microscopical sections originated from a later stage of i.p.

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