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HYALINOSIS CUTIS ET MUCOSAE (LIPOID PROTEINOSIS)

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Hyalinosis cutis et mucosae is a rare metabolic disorder of which nearly 80 cases have been described in the world literature. The condition seems to be fairly common in South Africa; 14 new cases are reported here, and 12 other South African cases are reviewed.

According to Laymon[1] the first case was described by Siebenmann in 1908. The names 'lipoidosis cutis et mucosae' and later 'lipid proteinosis' were given to this disease by Urbach. He thought that a primary lipoid metabolic disturbance was responsible, but lacked sufficient laboratory evidence. The name now generally accepted, 'hyalinosis cutis et mucosae' was first used by Wiethe and later by Lundt.[2]

Signs and Symptoms

The clinical signs are distinctive. Hoarseness is practically always the first symptom and is usually present at birth or develops shortly afterwards. The skin symptoms start as soon as the children start crawling and walking. Their skin is easily injured and they often suffer from recurrent attacks of severe impetigo. Depressed scars remain and at an early age the skin looks moth-eaten, as in atrophodermia vermiculata. As they grow older the skin shows severe scarring Figs. 1 and 3). Confluent papules develop on the exposed parts of the body. The axillae and elbow flexures show coalescent yellowish papules not unlike pseudoxanthoma elasticum (Fig. 7). The skin is yellow and feels infiltrated.

Hard infiltrated plaques develop on the lips. These are sometimes mistaken for leukoplakia. The anterior pillars of the fauces become nodular, hard and infiltrated. The same type of infiltration develops on the vocal cords and causes progressive hoarseness. Stricture of the larynx with asphyxia has been seen.

It may even become impossible to protrude the tongue as a result of the hard infiltrations on the sides and base of the tongue. The mucous membrane of the stomach may be affected. Many other abnormalities have been seen; e.g., swelling of the parotid glands, intracranial calcifications, dental abnormalities, diabetes, epileptic attacks, thinning of the hair, verrucous lesions on the hands and elbows (Fig. 2), mental deficiency etc. Consanguinity of the parents has been described in some cases.

A peculiar eye abnormality with macular atrophy has been described.[3-5]

Histology and Histochemistry

The epidermis is usually normal or shows slight thinning in the flat papules. There is hyperkeratosis and acanthosis in the verrucous areas. The basal layer remains intact. The most marked changes are seen in the dermis, where one finds many blood vessels and lacunae surrounded by homogeneous structureless masses which extend into the papillary layer (Figs. 4 and 5); the intimal cells of the vessels are compressed by hyaline material. The skin appendages are surrounded by the same hyaline material (Fig. 6).

According to most authors Sudan III gives a yellowish stain. According to Eberhartinger *et al.*[6] the reactions with Sudan III and Sudan black B are strongly positive especially around the skin glands. These authors concluded after ex-

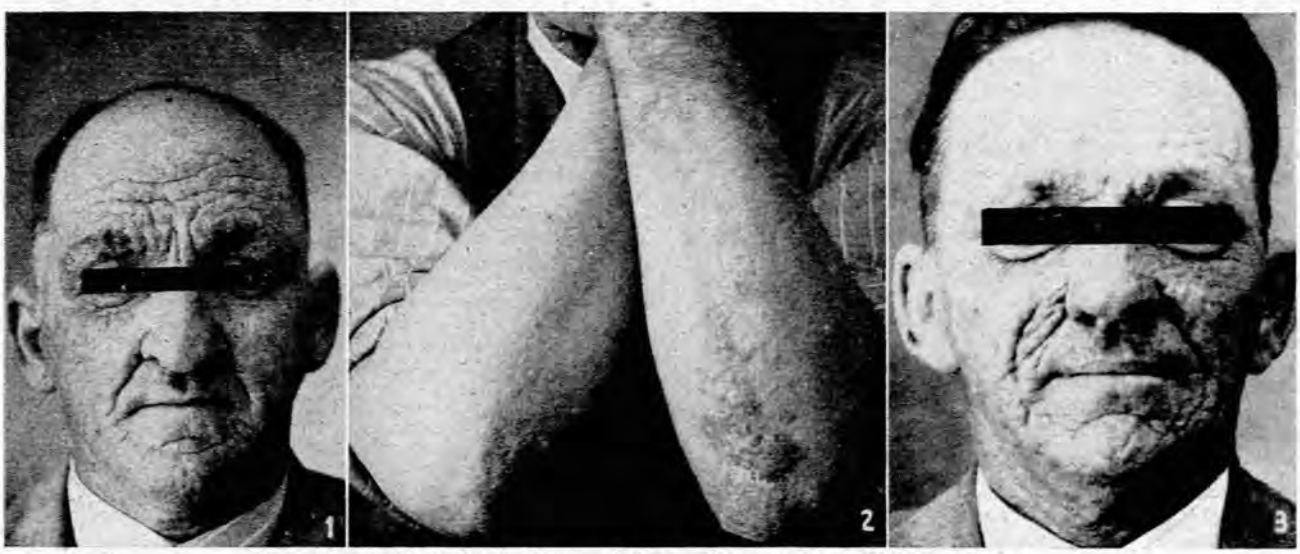


Fig. 1. Case 1. *Fig.* 2. Case 1. Verrucous lesions on elbows. *Fig.* 3. Case 2, brother of case 1.

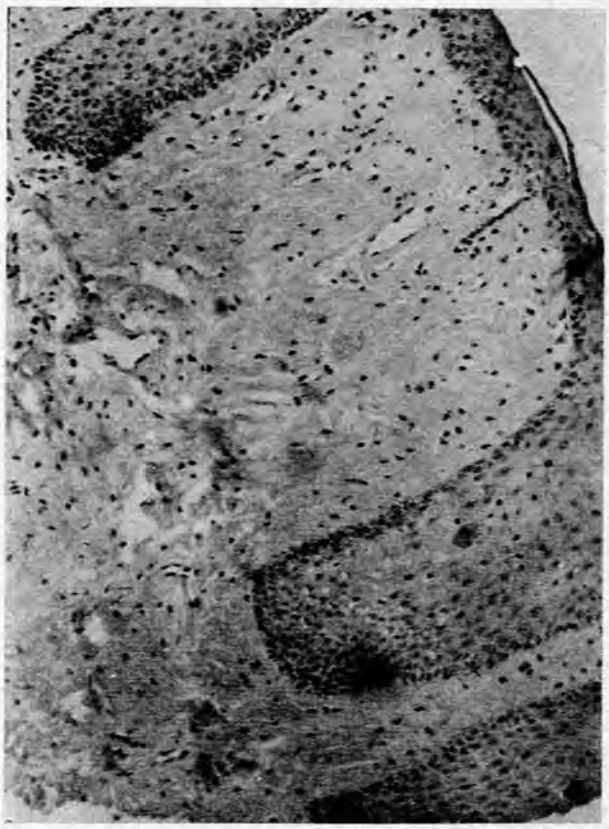


Fig. 4. Case 9. Structureless masses in epidermis. *Photomicrograph by Dr. E. v. Zinderen Bakker.*

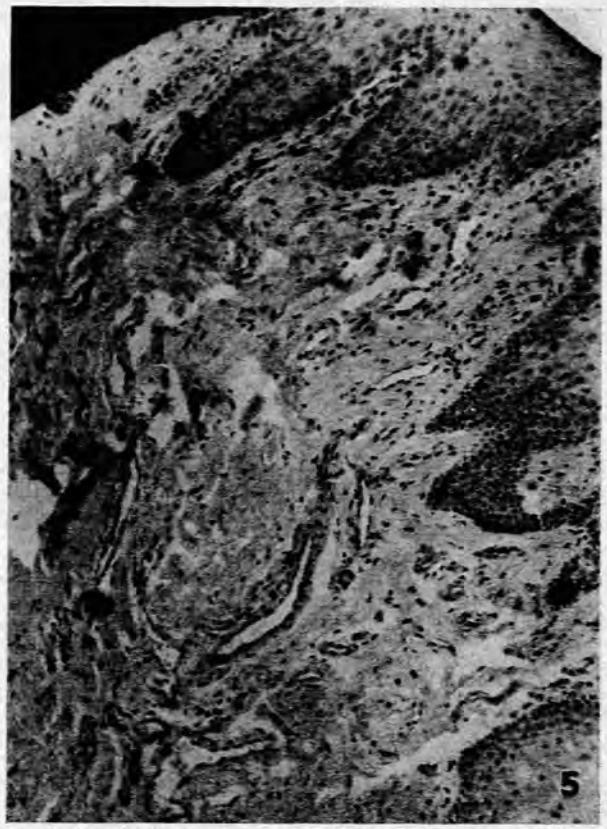


Fig. 5. Case 9. Structureless masses with lacunae and increase of blood vessels. *Photomicrograph by Dr. E. v. Zinderen Bakker.*

tensive histochemical studies that the homogeneous mass consists of a mixture of carbohydrate, lipoid and protein compounds. These are primarily deposited around the blood vessels and sweat glands. The elastic fibres disappear. Tests for amyloid are negative. The hyaline mass shows light blue-red colouring with eosin and yellow with v. Gieson, and reacts positively with periodic acid Schiff.

Mast cells occur in large quantities in the homogeneous masses and around the blood vessels and skin appendages.

With the silver carbonate method (Jabonero) Eberhartinger *et al.*[6] could demonstrate marked degenerative changes in the vegetative nervous system of the skin.

The walls of the blood vessels are infiltrated with the same homogenous mass and in certain areas, particularly around the sweat glands, complete obliteration takes place.

Blood Chemistry

Different findings have been reported by different authors. A raised blood sugar has been seen sporadically. The blood lipids are usually within normal limits. An increase in phosphatides was found in 10 of 16 cases examined.[7] Changes in serum proteins were only noted with electrophoretic studies. An increase in alpha and beta globulins and a decrease of albumin were reported.[7] Serum cholesterol is usually normal. The total lipoproteins and especially the S_F class 0 - 10 and 20 - 80 were also increased in the 2 cases examined by Eberhartinger and Reinhardt.[7] Lundt[2] reported an increase in fibrinogen. Porphyrinuria has been described.[2] Laymon[1] thought the hyaline material to be polysaccharide (amylase digestion followed by Hotchkiss-McManus staining). He also found an increase in total lipids and phospholipids. The erythrocyte sedimentation rate is often increased.

CASE REPORTS

N.B. In none of the following 14 cases was there any history of parental consanguinity.

Case 1

P.K., White male of an Afrikaans-speaking family, aged 50, had been hoarse since birth. He gave the typical history of recurrent impetigo and a tendency to traumatize easily since a very early age. For many years he has suffered from tiredness and swelling of the ankles.

On examination the typical signs of hyalinosis cutis et mucosae were found in a very severe degree, especially on the eyelids, mucosae of the lips, mouth, tongue and fauces (Fig. 1). Hair growth normal. No abnormalities seen in the fundus oculi. Many warty lesions on the hands and elbows. Sensitivity to pain was markedly decreased while that for touch was normal. The teeth were extracted at an early age.

A loud systolic murmur heard in the 2nd left interspace next to the sternum, accompanied by a systolic thrill, and a diastolic murmur. Liver slightly enlarged and tender. At the General Hospital, Pretoria, the condition was diagnosed as a patent ductus arteriosus.

A skin biopsy showed the typical features of hyalinosis cutis et mucosae.

Blood cholesterol and serum albumin and globulin within normal limits. Repeated negative Wassermann tests. The urine showed no abnormalities; no porphyrins detected.

X-ray skull: Marked calcification above the pituitary fossa on lateral view; no AP available.

Case 2

J.K., brother of case 1, aged 47, gave the same history and showed the same abnormalities of the skin and mucous membrane in a more marked degree (Fig. 3). There were no cardiac ab-

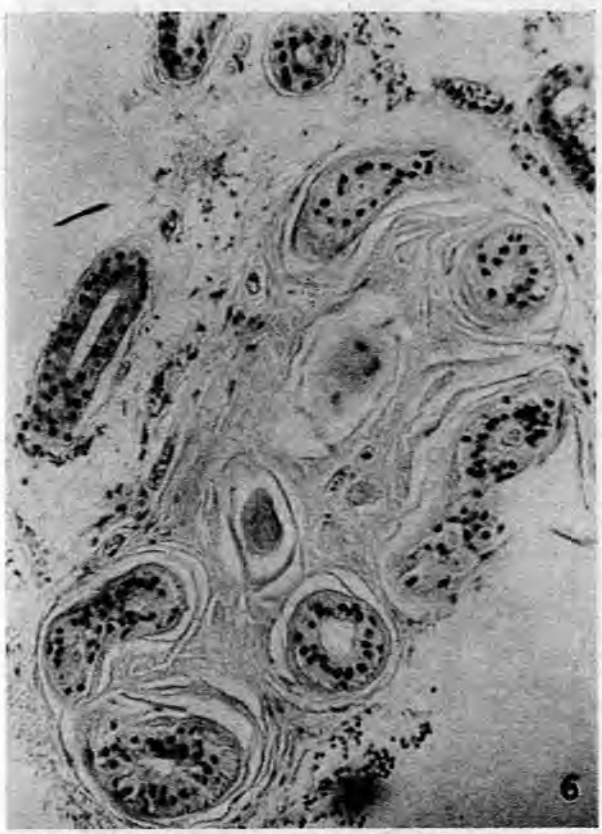


Fig. 6. Case 3. Hyaline masses surrounding sweat glands. *Photomicrograph by Dr. E. v. Zinderen Bakker.*

normalities but he had a typical pernicious anaemia, which has been treated in the usual way over the past 10 years.

Cutaneous sensitivity to pain markedly decreased. Sensitivity to touch intact. The teeth were extracted at an early age.

Histological examination showed the typical features of hyalinosis cutis et mucosae. Laboratory findings were negative, as with case 1.

X-ray skull: Marked calcifications in the same areas as case 1.

Case 3

W.vdW., an Afrikaans-speaking White male aged 27, gave the same history as cases 1 and 2 (Fig. 8). The hoarseness had recently increased to such an extent that it was almost impossible to understand his speech. Severe dysphagia as a result of ulceration of the fauces (Fig. 9).

Dr. J. G. Thomson, otolaryngologist, reported as follows: Teeth carious. Soft and hard palate, anterior and posterior pillars of fauces, and tonsils, exhibit large and small ulcers. The ulcers are superficial. The epiglottis and entire larynx are similarly affected. The walls of the nasal vestibules are thick, indurated and ulcerated.

Hair growth normal. No other internal abnormalities detected.

Histology: Typical hyalinosis cutis et mucosae. Hyaline degeneration very marked around the sweat glands (Fig. 6).

Eagle test negative. Cephalin cholesterol test ++, thymol turbidity 2·0, thymol flocculation negative, Takata-Ara no flocculation. Haemogram within normal limits. Glucose tolerance curve normal. Serum albumin 3·0%, globulin 3·7 g%. Blood urea 43 mg.%. Total lipid 461 mg.% (alpha 1 and 2 cholesterol 28%, cholesterol 72%).

Case 4

M.C., White female 8-year-old child of an Afrikaans family. Since the age of 4 months the parents noticed the hoarseness and recurrent impetigo, with depressed scars on the exposed parts. Hair growth normal. Dr. Thomson saw the child at the age of 2 years for the unusual voice and reported that the buccal cavity, pharynx, nasal cavities and ears revealed nothing of note, radiological examination of the chest showed only slight enlargement of the thymus, and direct laryngoscopy under general anaesthesia revealed no abnormal appearance; no diagnosis could then be made.

The child was seen again at the age of 8 years with the following findings: Bead-like deposits on the eyelids (Fig. 10) and a yellowish plaque on the lower lip and lateral wall of the left nasal vestibule. On indirect laryngoscopy the epiglottis was seen to be thick and folded and partly overhanging the glottis, and a thick white plaque was seen on the left ventricular band and left vocal cord, occupying the middle third of each. Urine: Albumin, sugar and porphyrins negative.

X-ray skull: Bean-like opacities in hippocampus area.

Case 5

S.C., brother of case 4, aged 4 years. The hoarseness started at the age of 6 months. He now has severe recurrent impetigo, and infiltrations with small white nodules are visible on the anterior pillars of the fauces. An elder brother and the parents are normal.

Urine: Albumin, sugar and porphyrins negative.

X-ray skull: No abnormalities.

Case 6

B. de V., White female 2½-year-old child of an Afrikaans family. The parents brought the child for treatment of recurrent impetigo which left ugly scars. She had been hoarse since birth.

The lower lip was markedly infiltrated and there was much bead-like scarring of the eyelids. Hair growth sparse.

Urine: Albumin, sugar and porphyrins negative.

Case 7

Sister of case 6, 6 months old. The patient had been normal hitherto, but the voice was becoming hoarse and impetigo had started on the face and hands. No other members of the family affected.

Except for the hoarseness and a few spots of impetigo no abnormalities could be detected. Hair growth normal.

Case 8

M.L., White female 2-years-old child. Both parents of British descent. The child was hoarse from birth. At about 18 months she developed recurring attacks of impetigo which left depressed scars.

Hair growth very sparse and hair shafts thin and lustreless.

Urine: Albumin, sugar and porphyrins negative.

Case 9

E.V., White female, 15 years old. Hoarse since birth.

Bead-like scarring of eyelids. Hard infiltrated plaque on lower lip. Skin otherwise normal apart from mild acne vulgaris. Indirect laryngoscopy (Dr. Thomson) showed no unusual appearance of the hypopharynx; the vocal cords seemed short, hypertrophic and thickened; no apparent abnormal motility; anterior and posterior rhinoscopy and otoscopy showed nothing unusual. Urine: Albumin, sugar and porphyrins negative.

Histological examination of patch on lip showed marked hyaline degeneration of the cutis (Fig. 5).

Case 10

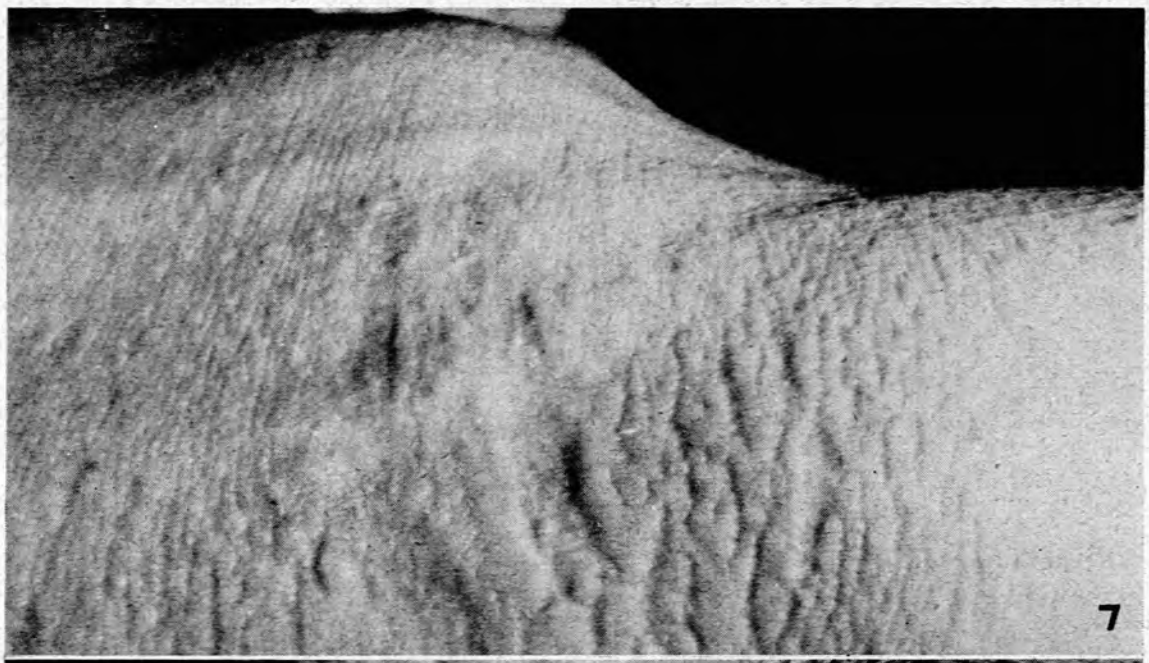
White male 16 years old, of an Afrikaans family. Hoarse from birth and developed vesicles and impetigo at an early age. All the teeth had been extracted for caries. Hair of scalp sparse since birth. No relatives affected.

Eye trouble since the age of 7. Wax-like, transparent texture of skin of face and arms. Severe ankyloglossia. Bead-like infiltration on eyelids. Severe scarring and papular infiltration on forehead. Acne-vermoulante-like atrophy of forehead and cheeks. Infiltration of both lips.

X-ray skull: calcifications in hippocampal area (Fig. 13).

Fundi: Dr. Neville Welsh kindly reported bilateral macular changes, probably a type of macular dystrophy—small, dark pigmented spots equally distributed in the macular region of both eyes (Fig. 11). In the right eye only there was also an area extending from 9 to 2 o'clock above the posterior pole one disc diameter away from the disc and the macula, and consisting of a white streak, irregular in shape, with patches of pigment overlying it in places; the retinal vessels pass anterior to it and the vessels are normal (Fig. 12). Remainder of fundus normal. Vision less than 6/60 in each eye. Dr. Welsh's diagnosis was 'retinal degeneration ? vascular in origin, i.e. choroidal vessels; ??? Coats's disease'.

Histology: Typical hyalinosis cutis. Scharlach-red reaction strongly positive (Fig. 14).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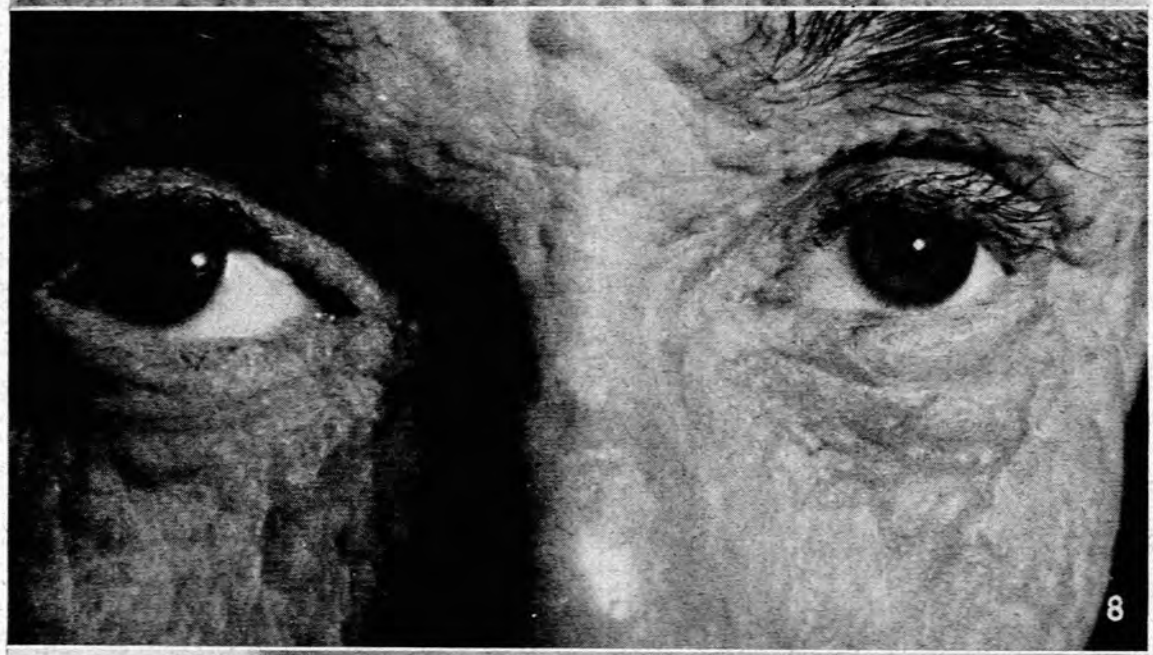
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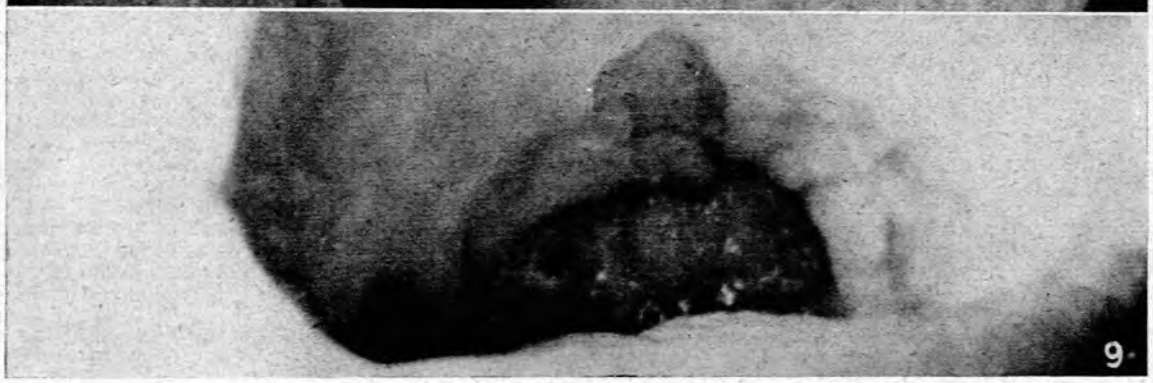
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Case 11

V.E.K., Afrikaans-speaking White male 28 years old. Hoarseness and skin lesions started at the age of 4 months. Skin shows the typical changes with involvement of the lips, eyelids and mucous membranes. Slight ankyloglossia, with sclerosis and induration of the edges. Warty growths on the palms. Pharynx also affected. Sensitivity for pain decreased.

Blood: Cholesterol 269 mg.%, albumin 4·42 g.%, alpha$_1$ globulin 0·18 g.%, alpha$_2$ 0·46, beta 0·80, gamma 1·44. Urine: Albumin, sugar and porphyrins negative.

X-ray skull: Calcifications on lateral views just above the pituitary fossa—not distinct on the AP view.

Case 12

H.K., age 19, brother of case 11. Hoarseness and skin trouble since the age of 1 year. No other members of family affected.

Abnormalities of skin and mucous membrane similar to those of his brother. The sensitivity for touch is slightly reduced while that for pain is definitely diminished.

Blood: Cholesterol 244 mg.%, albumin 4·6 g.%, alpha$_1$ globulin 0·21 g.%, alpha$_2$ 0·37, beta 0·84, gamma 1·28. Urine: Albumin, sugar and porphyrins negative.

X-ray skull: Calcifications in the same positions as in case 11.

We wish to thank Dr. James Marshall for the special investigations of cases 11 and 12.

Case 13

J.W. duT., Afrikaans male 29 years old. Whispering voice from birth to the age of 10, when there was a temporary improvement of the voice for a few years. Skin abnormality started at the age of 6 months; there was much festering of the wounds, which occurred on all parts of his body; his mouth was also affected. At the age of 18 he suffered from a possible oil acne of the neck as a result of his work as an engineer.

Seen by Dr. Thomson in 1953. Indirect laryngoscopy then showed ulceration on the tip of the epiglottis, with flat papillomata on the edges of the ulcer, papillomata on the interarytenoid space, and good motility of the vocal cords. No history of abnormalities in the family; a non-identical twin brother is normal.

X-ray skull: Bilateral temporal-lobe calcifications of the exact position and size described in lipid proteinosis. The pineal calcified and central in position. No other cranial abnormalities.

Electro-encephalogram: No definite abnormalities present. Technically somewhat unsatisfactory records; moderate voltage, and well-developed symmetrical parieto-occipital 10 - 11 second rhythms; reaction with opening eyes. Considerable fronto-temporal low-voltage 4 - 6 per second theta activity, somewhat predominating in the left temporal region (Dr. A. M. Theron).

Histology: Typical appearance of lipid proteinosis in sections stained with H & E and with Sudan IV.

Blood: Cholesterol 199 mg.%, alpha-lipoproteins 20·1% and beta lipoproteins 79·9%.

Case 14

Male aged 19. English father, Afrikaans mother. Skin of hands traumatizes easily. Also complains of an abnormal sensitivity of the hands and feet to sunlight, which is worse during March, and thickening of the knuckles. No hoarseness. Family history negative.

Hands look like those of an elderly person. Small irregular papules on forehead. Mucous membranes normal. He gave the impression of slight backwardness. Urine: Porphyrins negative. X-ray skull: No intracranial calcifications. EEG: No foci or any specific abnormality.

The following cases have been seen and/or previously reported in South Africa:

Case 15 (*Case of Dr. L. J. A. Loewenthal*[9])

White female 22 years old of Afrikaans stock. Mild hypochromic anaemia. Urinalysis negative. Blood sugar 83 mg.%. Serum cholesterol 180 mg.%, Kahn test negative. Histology: Typical proteinosis.

Case 16 (*Case of Dr. Loewenthal*[9])

White female 35 years old, of Afrikaans family. Hoarse since infancy. Thickening of tongue. Haemogram normal. Serum cholesterol 150 mg.%. Urinalysis negative. Histology: Typical lipid proteinosis.

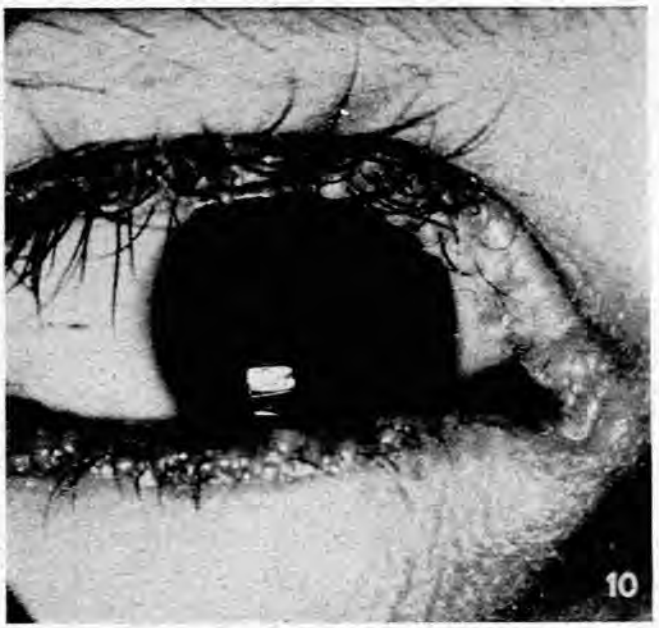

Fig. 10. Case 4. Bead-like deposits, eyelids. *Photograph by Dr. Gordon Trichardt.*

Case 17 (*Case of Dr. Loewenthal*[10])

Afrikaans female 16 years old. Hoarseness and skin lesions started at the age of 18 months.

Case 18 (*Case of Dr. C. M. Ross*[11])

White male 23 years old, of Afrikaans family. Voice became hoarse before puberty. Two sisters affected (cases 19 and 20); 2 children normal; no parental consanguinity, but maternal grandparents were first cousins; maternal grandfather's sister was blind from birth and very hoarse; one of his brothers was blind and suffered from attacks of parotid obstruction.

Blood sugar and blood count normal. No serological evidence of syphilis. Free cholesterol, total cholesterol, and alpha and beta lipoproteins within normal limits.

This patient was subsequently seen by us. The sensitivity for pain was found to be diminished in the affected areas of the face. X-ray of skull showed extensive calcification in the hippocampus area.

Case 19 (*Case of Dr. Ross*[11])

White female aged 46 (sister of cases 18 and 20). Hoarse since birth and lesions on elbows. Hair became sparse at age of 36 and nodules on eyelids developed at age of 44. Two normal children.

Blood sugar and blood count normal. No serological evidence of syphilis.

Case 20 (*Case of Dr. Ross*[11])

White female aged 43 (sister of cases 18 and 19). Skin lesions and hoarseness since birth.

Blood sugar and blood count normal. Normal total lipoids. No serological evidence of syphilis.

Case 21 (*Case of Dr. Ross*[11])

White female aged 33, of Afrikaans family. Hoarseness and skin lesions developed at age of 33. No parental consanguinity Seven normal siblings.

Blood sugar and blood count normal. No serological evidence of syphilis.

Case 22 (*Case of Dr. Findlay*[12])

White male 19 years old, Afrikaans family. All known relatives normal. Since age of 8, repeated swelling and burning of hands. Heat and sunlight caused subjective burning.

Elastotic hands like an aged labourer. Face pale and sclerotic with vermiculate atrophy. Intellectually slow, perseverating, with labile moods. No mucosal involvement. Punch biopsies were done painlessly without local anaesthesia. No fat with Sudan III stain. Gamma globulins and sedimentation rate slightly raised. Serum mucoproteins, blood count and liver functions normal. Histology: Typical hyalinosis cutis.

Fig. 7. Case 3. Papules and atrophy in axilla suggesting pseudoxanthoma elasticum. *Fig.* 8. Case 3. Degenerative skin changes, face and eyelids. *Fig.* 9. Case 3. Ulcer on the fauces.

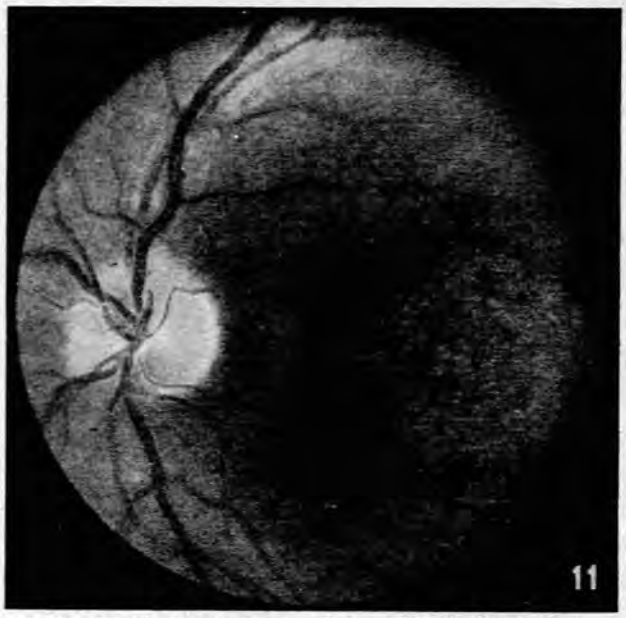

Fig. 11. Case 10. Macular change. *Photograph by Dr. Hennie Meyer.*

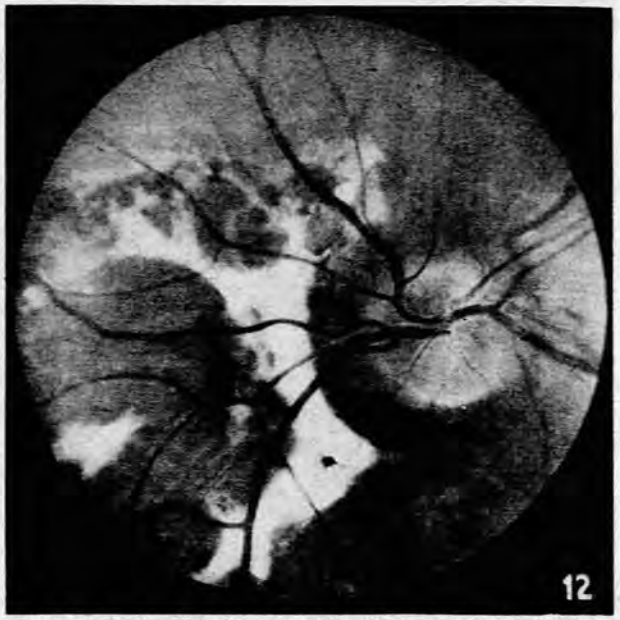

Fig. 12. Case 10. White irregular streak with pigment patches, right eye. *Photograph by Dr. Hennie Meyer.*

Case 23 (*Case of Dr. H. Klevansky*)

B.M., Afrikaans female aged 8 years. The child had a peculiar voice since birth. The mother noticed at the age of about 10 months that the skin was thickened and red, especially over the dorsa of the hands, knees and elbows. There are 3 other children, with no skin trouble. The parents are not related.

A biopsy was performed which confirmed the clinical diagnosis of lipoid proteinosis. Numerous tests have been performed for porphyrins on the urine and stools with negative results.

Case 24 (*Case of Drs. J. J. Walker and R. Kooij*)

A Coloured female, whose great-grandfather was a German, became hoarse at the age of 9 years. Sores and scarring developed on the exposed parts. Tongue and eyelids are also involved. No parental consanguinity.

Wassermann test negative. Blood urea, liver function tests, serum albumin, cholesterol and calcium within normal limits.

Case 25 (*Case of Drs. Walker and Kooij*)

A Coloured female aged 13, sister of the previous case. History, clinical findings and blood chemistry essentially the same.

Case 26

Another typical case was seen in consultation by the authors in 1953. The patient was an Afrikaans lady of 23, and had been delivered of a normal infant. No investigations were made at the time, and it has since been impossible to trace her.

DISCUSSION

No cases were seen in pure Bantus. Cases 24 and 25 are Coloured sisters with a German great-grandfather. The parents of case 8 are both immigrants from the U.K. All the other cases belong to Afrikaans-speaking families, bearing well-known Afrikaans surnames, a few of whom were also known to have German forefathers. The apparent rarity of the disorder in Britain suggests a genetic tendency derived rather from the European continent, which has become widespread in the South African population descended from that stock. Present-day evidence from Europe points to the German-speaking countries as the most probable source.

The incidence of hyalinosis cutis et mucosae seems to be fairly high in South Africa, and general practitioners and otolaryngologists could well bear this anomaly in mind when hoarseness is the only complaint in young children.

The clinical picture is usually very typical, and other internal manifestations are often seen. No diabetes and no porphyria were detected in the South African cases. One patient (case 1) suffers from congenital heart disease; his brother (case 2) has pernicious anaemia.

The eye complications of case 10 are unusual. They seem to differ from the fundus abnormalities described by other authors.[3-5]

The lowering of cutaneous pain sensitivity in several cases, first described by Findlay[12] (case 22), is difficult to explain, but has been confirmed in subsequent cases. The severe scarring might be partly responsible for this.

Intracranial calcifications in the region of the hippocampus were seen in 7 of the 9 cases examined radiologically. It is not yet certain whether these calcifications are in the brain substance, as Eberhartinger and Niebauer[6] believe, or whether

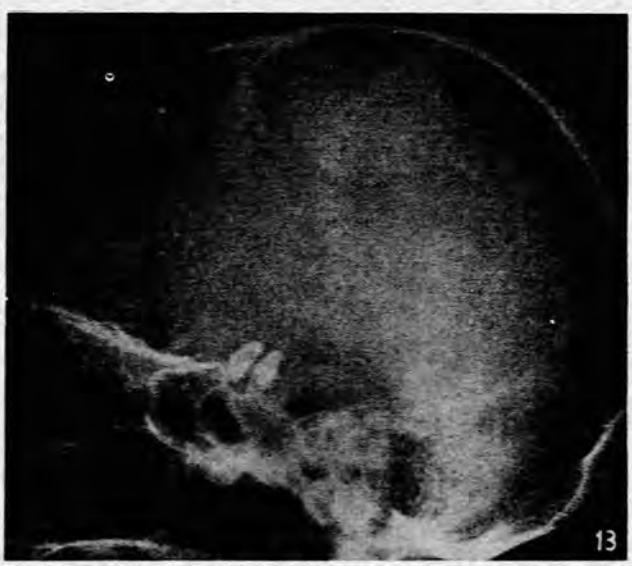

Fig. 13. Case 10. Calcifications in hippocampus area.

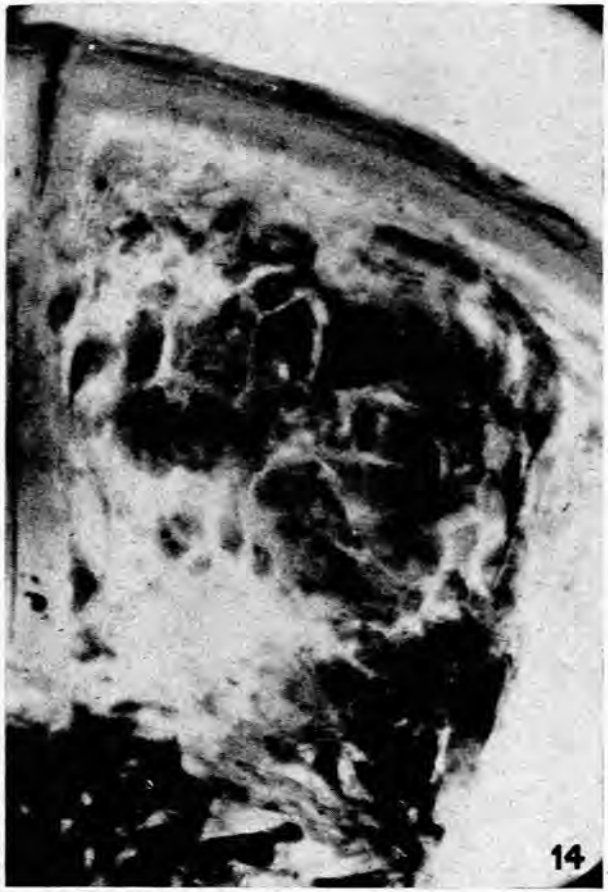

Fig. 14. Case 10. Positive Scharlach-red reaction.

they are localized in the dura or cerebral vessels. Except in one case, where there was slight mental retardation, no epilepsy or other gross mental abnormalities were seen in our cases. Epilepsy and mental deficiency, however, have been described by other authors.[5]

The skin complications are mainly limited to the exposed areas. Sunlight seems to aggravate the condition. It cannot, however be the primary cause because the early development of mucous-membrane symptoms is against such a theory.

More histochemical and particularly lipoprotein studies seem to be necessary to clarify the pathogenesis of this disease. South Africa undoubtedly offers enough material for such a study.

Treatment

In cases 1 and 2, temporary subjective improvement was experienced with Fowler's solution and fat-free diet. There was much improvement of the hoarseness in case 3 with aralen. Steroids were of no avail in several cases in which they were tried. Intradermal injections of hydrocortisone acetate and hyaluronidase in localized areas brought about no improvement.

SUMMARY

A review is given of 26 cases of hyalinosis cutis et mucosae seen in the Union of South Africa. Congenital heart disease and pernicious anaemia are internal manifestations not previously described. The attention of general practitioners and otolaryngologists is drawn to the primary and often for long the sole complaint, viz. *hoarseness*. The significance of another symptom, viz. decreased cutaneous sensitivity to pain, is not clear.

We wish to thank Dr. D. J. J. Bezuidenhout for his help in the preparation of the photographs.

ADDENDUM

While this article was going to press a further case of lipid proteinosis was seen in a 10-year-old girl. She was the eldest in the family, which comprised 3 normal siblings. The 4 grandparents had different well-known Afrikaans surnames, and no German ancestors were known. Ever since babyhood the child has had attacks of a severe subjective burning sensation of the hands or feet, lasting a few days at a time, unassociated with swelling or redness. This, which was the main complaint, was reminiscent of case 22. The face showed depressed and linear scars from old impetigo and scratches, and the distal parts of the extremities showed a thickening with sclerosis, the hands appearing old and weather-beaten. There were no apparent circulatory, mucosal, psychic or neurological changes. Diagnosis was confirmed by skin biopsy.

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