CASE OF LIPOID PROTEINOSIS

BY

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Lipoid proteinosis (Urbach-Wiethe disease; hyalinosis cutis et mucosae) is a rare and striking disorder in which there is a peculiar infiltration of the skin and mucous membrane. Siebenmann (1908) described a case of "ichthyosiform disease" in a 19-year-old girl under the subtitle of "hyperkeratosis cutis universalis, keratosis oris, linguae, labiorum, palati duri et mollis, arcuum et tonsill. pal. epiglottidis et laryngis." His was probably the first clinical description of lipoid proteinosis. Between 1924 and 1929, Urbach and Wiethe (1929) collected nine cases occurring in four families and established this condition as a clinical entity.

Lipoid proteinosis affects the sexes equally, and is often familial, particularly if there is consanguinity. A "diabetic tendency" in the patient and a family history of diabetes mellitus have been reported. These patients usually give a history of hoarseness dating from infancy; the associated laryngeal changes are often progressive and may necessitate tracheostomy. Skin changes, in various forms, appear constantly by the age of 12 years. The scalp shows diffuse non-scarring alopecia. Nodular lesions occur on the lid margins; on the face, where they may lead to pock marks; and on the elbows and knees, where they may progress to form warty hyperkeratotic plaques. There are infiltrated plaques at the angles of the mouth and in the gluteal cleft, which may become deeply fissured and infected. Mauve atrophic patches may be found on the face; and perifollicular atrophy of the neck and upper arms produces an appearance reminiscent of pseudoxanthoma elasticum. Attacks of stomatitis and parotid swelling are described. Similar changes involve the mucous membranes of the nose, mouth, pharynx and larynx, and the vagina and anal canal. Any of the above features may be absent.

The clinical aspects, pathological findings, and literature have been well reviewed recently (Laymon and Hill, 1957; Eberhartinger and Niebauer, 1959; Ungar and Katzenellenbogen, 1957). Ramos e Silva (1943) described two additional features found in this condition—petechiae of the face and endocranial calcification, which he thought occurred in dural folds. By 1959 endocranial calcification had been found in 8 out of 18 patients with lipoid proteinosis in whom x-ray examination of the skull had been carried out, and two of these suffered from epilepsy. Eberhartinger and Niebauer thought that the calcification in their two patients was in the brain substance. Since then eight further cases of endocranial calcification have been described—four "above the pituitary fossa," three "in the hippocampus," and one "in the temporal lobes" (Scott and Findlay, 1960). No epilepsy, however, was noted by these authors.

About 100 cases of lipoid proteinosis have now been reported, but we believe the following case to be the first in Great Britain. This case is of special interest in that intermittent bruising, with a strongly positive tourniquet test, was present. The histological findings indicate that there are grounds for believing that increased capillary fragility plays an important part in the pathogenesis of this condition.

Case Report

A 42-year-old housewife was first seen in the skin department in June, 1958, having been referred by the E.N.T. surgeons. Her appearance was striking—a tall, thin, pale woman with sparse hair and a "plucked chicken" appearance of the skin of the neck. She talked in a hoarse whisper. Known to be an epileptic, she was taking phenytoin sodium. A provisional diagnosis of pseudoxanthoma elasticum was made, although no angioid streaks of the retina were seen. The diagnosis of lipoid proteinosis was suggested on histological grounds by Dr. A. H. T. Robb-Smith.

On re-examination it became obvious that hers was a classical example of this condition. It began in infancy, when she always cried silently, and even when red in the face with rage she seemed unable to make a noise. At the age of 12 years she developed a lesion on her left shoulder, diagnosed as a "ringworm," which has remained, leaving a heaped-up scarred area. At the same time she noticed the beginning of skin changes of the neck. She was quite sure that at the age of 10 years her skin was normal, and that by the age of 12 it had its present appearance. In her thirties she developed "blackouts" and was diagnosed as having akinetic epilepsy by Dr. C. W. M. Whitty in 1956. Neurological examination revealed nothing abnormal. An electroencephalographic report stated: "Very low voltage record showing paradoxically some 10 c/s alpha rhythm over the anterior part of the head only. Some 18 c/s low-voltage activity is more diffuse. No change on over-breathing. No sign of epileptic action. Probably normal."

Her epilepsy was well controlled when she took phenytoin $\frac{1}{2}$ gr. (50 mg.) t.d.s. Otherwise she had always been well and had had no serious illnesses. She did, however, suffer from migraine.

Her periods, which began at the age of 14, were scant and irregular until 1956, when they became heavy but regular, and she complained of flooding. This was regarded by the gynaecologists as "dysfunctional endocrine bleeding of a mild nature." Dilatation and curettage was refused by the patient, as it could not be guaranteed to be curative. At the same time as the "flooding" she also developed an increased tendency to bruise. She was seen in the ear, nose, and throat department in 1956 by Mr. R. G. Macbeth on account of her hoarseness, and was found to have thickening of the false vocal cords.

She was an only child. Her mother developed diabetes mellitus in middle age, but her father and six aunts and uncles were all well. She had four children, one of whom had flexural eczema. There was no other family history of diabetes mellitus, epilepsy, skin disease, or consanguinity, but her paternal grandmother had been hoarse.

Examination in September, 1958, showed a middle-aged woman with diffuse non-scarring alopecia, most pronounced in the occipital region (Fig. 1), whose hair was brittle and dry. Her face was waxy, deeply wrinkled, and immobile (Fig. 2). On the right side of the forehead she had a slightly atrophic mauve lesion. Her eyebrows were normal, but the eyelashes were scanty, and the upper lid margins were studded with pearly, bead-like lesions. The margins of her nostrils were thickened and she had infiltrated plaques at the corners of the mouth, with fissuring. On the neck, chest, upper arms, and, to a less extent, on the forearms there were yellowish follicular papules with slight perifollicular atrophy. The skin had an "elastic" feel which was

noticed particularly on biopsy. Warty, hyperkeratotic, shiny plaques were present over both elbows, with a small excrescence on the left (Fig. 3). On the left shoulder there was a lesion 1 in. (2.5 cm.) in diameter, pale and wrinkled, with perifollicular atrophy and some infiltration. In the gluteal cleft she had an infiltrated, reddish, puckered lesion. The vulva, vagina, and anus were normal. Widespread bruising was present, and a tourniquet test for capillary fragility was strongly positive.

There was crusting of the vestibules with some stenosis of both nostrils. The nasal mucosa showed moderate atrophic rhinitis. The pharynx and post-nasal space were normal. At indirect laryngoscopy only half the larynx was visible and the patient appeared to phonate with the false vocal cords. Direct laryngoscopy and bronchoscopy by Mr. R. G. Macbeth showed that the posterior halves of both vocal cords were thickened and "knobby." The tissue in this situation was white in colour. There was some thickening over the arytenoids in the interarytenoid region. The epiglottis, aryepiglottic folds, and subglottic regions were normal. A biopsy was taken. The bronchi appeared normal. General examination was otherwise normal.

FIG. 1

FIG. 1.—Photograph of patient, showing area of alopecia.

FIG. 2

FIG. 2.—Face waxy, deeply wrinkled, and immobile.

FIG. 3.—Showing warty hyperkeratotic plaques on elbow.

After diagnosis and further investigation, treatment with prednisolone 5 mg. t.d.s. was begun in September, 1958. One month later her voice was louder, and skin changes were less marked. There was practically no bruising and the tourniquet test was only weakly positive. By January, 1959, the skin had continued to improve and felt less "elastic" and infiltrated; there was no bruising, and a tourniquet test was negative. However, steroid therapy was tapered off in May, 1959, as she was developing rosacea-like pustules. There was little change until July, 1960, when she was found to have non-tender swelling of the left submandibular gland, lasting for one month. She had been a mumps contact. During the last 12 months the voice has deteriorated. She has had increasing dyspnoea, her hair has become sparser, and her skin has remained the same.

A further ear, nose, and throat examination showed an advanced degree of vestibular stenosis on both sides. The pharynx was dry with some reddish discoloration of the soft palate and submucosal infiltration. Indirect laryngoscopy showed considerable thickening of both vocal cords. The larynx was pale, with scarring and some proliferation posteriorly. Some oedema of the arytenoid region was present. The tourniquet test in October was weakly positive. Cineradiographic examination confirmed extensive involvement of the larynx (to be reported later).

Investigations.—Initially, in 1958, the following tests were carried out: haemoglobin, 91% (Haldane); white-cell count 7,600/c.mm. (normal differential count); platelets, 235,000/c.mm.; bleeding-time (Ivy) 4, 5, and 6½ minutes. Capillary microscopy of the skin showed nothing abnormal. The tourniquet test was strongly positive and this was thought to be sufficient to account for the abnormal bruising. The direct Coombs test was negative in all dilutions using three different Coombs reagents. Wassermann and Kahn reactions were negative. Total blood serum proteins were 6.5 g./100 ml. (albumin 4.5 g., globulin 2 g.) and paper electrophoresis showed a normal pattern. Blood cholesterol was 200 mg./100 ml. and blood lipid phosphorus 5.2 mg./100 ml. Urine examination was normal. These tests have remained normal on repeated examination.

Radiological Examinations

Chest: normal.

Sinuses: "Sinuses appear clear. Bilateral intracranial opacities projected over antra in occipito-mental view—? nature."

Skull (report by Dr. P. W. E. Sheldon): "There are solid calcifications overlying the pituitary fossa in the lateral view, but lying about 2.5 cm. from the midline on either side. These are not like dural calcifications, nor do they resemble carotid calcification. They appear to be free from any bone, and must lie somewhere in the region of the anterior parts of the hippocampi or in the amygdaloid nuclei (Fig. 4). However, I am at a loss to explain their precise nature, at least without air studies." Electroencephalogram in 1960 showed "low-amplitude record with a fair amount of symmetrical 10 c/s alpha rhythm in the post-central region. It remains stable on overbreathing. Normal record."

Histology

Biopsy specimens were taken from a nodular area at the posterior end of a vocal cord and from an infiltrated area of skin. These were fixed in neutral formal-saline, and, since they were small and the diagnosis was not suspected, they were embedded entire in paraffin.

The laryngeal biopsy was covered by rather flattened squamous epithelium without hyperkeratosis. In the stroma were large homogeneous areas, usually with comparatively smooth sides and ragged ends, suggestive of degenerate collagen (Fig. 5). They showed no fibrillar pattern and nuclei were scanty, most of those present being of the endothelium of narrow slit-like capillaries. These hyaline areas were brightly eosinophil and a few lymphocytes lay around their margins. In the adjacent stroma many of the capillaries were surrounded by a narrow sharply defined concentric layer of similar hyaline material immediately outside the endothelium (Fig. 6). The same change affected the media of a few small arterioles and surrounded the duct of a mucous gland, the epithelium of which showed squamous metaplasia. The skin biopsy showed flattening of the epidermis with small widely separated rete pegs. Discrete areas of structureless eosinophil material lay in the dermis similar to those in the larynx. Perivascular hyaline

material was also present, and a narrow layer surrounded some of the sweat glands, which showed no atrophic changes. With van Gieson's stain, the hyaline material in both biopsies varied from yellow to the khaki colour which suggests, but is not diagnostic of, amyloid. The results with Congo red and methyl violet were negative for amyloid. Argyrophil fibres were plentiful in the superficial dermis except in the hyaline areas. These were entered by a few fine fibrils, but the dermic reticulin pattern was lost within them. No reticulin was seen in the perivascular or periglandular hyaline material, which appeared to be within the basement membrane.

No orcein-positive material was present in some of the hyaline areas. Others contained irregular clumps or short fragments of coarse fibres. Elastica throughout the rest of the laryngeal biopsy was coarse, clumped, and irregular in disposition. The dermic elastica at a distance from the hyaline areas was not strikingly abnormal, but irregularity, clumping, and variation in calibre and staining intensity were prominent in their immediate vicinity. The hyaline material gave a strongly positive periodic-acid/Schiff reaction, unaffected by amylase digestion. Dilute aqueous toluidine blue and thionine both gave a streaky metachromatic reaction. No sudanophil material was preserved in the paraffin sections.

Another biopsy was made of skin taken from a less severely affected area and fixed in Baker's formalin solution with calcium chloride and cadmium chloride. There were small patches of diminution of dermic elastica and others of coarse, clumped, irregular fibres, usually around blood-vessels. Narrow hyaline haloes surrounded some of the capillaries and sweat glands, but no large hyaline areas were present. Frozen sections stained with Sudan black revealed fine lipid droplets localized in zones of degeneration of elastica. Fewer droplets were seen in sections stained with Sudan IV. Baker's acid-haematin method gave a negative result. The melanophores of the superficial dermis contained numerous droplets which stained with Sudan IV and Sudan black, and gave a deep-blue colour with Nile-blue sulphate. Dermic mast cells were very conspicuous in this biopsy, although not so frequent as to be clearly of pathological significance.

Discussion

Most of the classical features of lipoid proteinosis were present in our patient. The following were absent: parental consanguinity, diabetes mellitus in the patient, pock marks on the face, and involvement of the vaginal

FIG. 4.—Calcified lesions in lateral skull x-ray film.

FIG. 5.—Biopsy of vocal cord. (Haematoxylin and eosin. $\times 100$.)

FIG. 6.—Biopsy of vocal cord. (Haematoxylin and eosin. $\times 200$.)

and anal mucosae. She was edentulous at the first visit, and we were unable to find out if she had any dental abnormality, such as has been described by various authors (Gerth and Flegel, 1956). The salivary-gland enlargement, which has previously been described, was unlikely to be mumps, even though she had been a contact, as the clinical course was dissimilar.

Since 1943 endocranial calcification has been noted in some of these patients, and fits, thought to be associated with it, occurred in two cases. The calcification appears to be in the temporal lobes, even in Ramos e Silva's (1943) case. Our patient had bilateral calcification in the temporal lobes, probably medial to the posterior horns of the lateral ventricles; but it was not considered justifiable from the patient's point of view to confirm this by air studies. Her fits were diagnosed as akinetic epilepsy; there was no auditory or gustatory aura as might be expected in temporal-lobe lesions, and electroencephalograms were normal.

The marked bruising tendency with a positive tourniquet test has not previously been described in lipoid proteinosis. It was suppressed completely while she was taking corticosteroids. Probably her menorrhagia was an associated phenomenon. Full investigation of the purpura revealed only increased capillary fragility. This could be explained by the widespread deposition, in and around capillaries, of eosinophilic staining material, rather analogous to primary systematized amyloidosis.

The histological findings leave no doubt that our patient has the same disorder as that described by Laymon and Hill (1957) and by Ungar and Katzenellenbogen (1957), although the changes are less advanced than those described and illustrated in the latter paper. We cannot help to elucidate the nature of the hyaline material, which in its perivascular distribution bears a resemblance to amyloid but in its staining properties shows wide differences. The localization of lipid to the degenerate orcein-positive fibres appears significant, and, so far as they go, our findings seem to support those of Ungar and Katzenellenbogen.

Lipoid proteinosis has been regarded as a systemic disease because of the presence of eye changes (Holtz and Schulze, 1950; Gerth and Flegel, 1956; Scott and Findlay, 1960), association with diabetes mellitus (Urbach and Wiethe, 1929; Tompkins and Weinstein, 1954), testicular involvement (Bazex, 1939), intracranial calcifications and bromsulphthalein retention (Wile and Snow, 1941; Price *et al.*, 1947).

Diabetes mellitus was found only as an associated feature in early cases, and the testicular involvement (Bazex, 1939) took the form of deposition of sudanophilic material around blood-vessels. A degree of bromsulphthalein retention is insufficient by itself to enable liver involvement to be postulated; and liver biopsy of two cases showed normal histology (Tompkins and Weinstein, 1954). Extensive skeletal x-ray films of one case (Price *et al.*, 1947) were normal. Full investigation of several cases has not borne out this possibility.

A study of the literature indicates that, unlike primary systematized amyloidosis, the prognosis of lipoid proteinosis is good; the only potentially lethal complication being laryngeal obstruction. Corticosteroids have proved beneficial to skin and laryngeal lesions in our case and one of Eberhartinger and Niebauer's; early and prolonged administration may be of benefit.

Summary

The first British case of lipoid proteinosis of Urbach and Wiethe is described. In addition to the usual features the patient had an increased tendency to bruise, probably caused by infiltration of blood-vessel walls.

Histopathology and histochemistry support the hypothesis that the disease is primarily an infiltrative process.

Early and prolonged corticosteroid therapy may be of benefit.

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A STUDY OF 65 CASES OF COMPOUND PRESENTATION

BY

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Although a few isolated cases of compound presentation have been reported in recent years (Claye, 1929; Wong, 1932; Henderson, 1952; King and Mitchell, 1953; Bowles, 1954; Anderson, 1955; Alderman, 1958), only two studies of relatively large series of cases have been presented in the English language—namely, one by Goplerud and Eastman (1953) and the other by Quinlivan (1957). The former made a survey on 65 cases and the latter on 33. A study was therefore made of the 65 cases which occurred in the Tsan Yuk Hospital, Hong Kong, over a period of 14 years (1946 to 1959). Compound presentation is said to occur when one or more extremities, an arm, a leg, or both, prolapse alongside a head which presents, or when one or both upper limbs prolapse alongside a presenting breech.

Incidence

The incidence as shown in the German literature in the nineteenth century varied between 1:1,956 and 1:64 (Pernice, 1858). McCormick (1947) gave an incidence of 1:250, Gibberd (1951) one of 1:800, Goplerud and Eastman (1953) one of 1:652, and Quinlivan (1957) one of 1:360 in St. James' Hospital, London, and one of 1:500 in Hillingdon Hospital, Uxbridge, Middlesex.

In the years 1946 to 1959 inclusive there were 85,879 deliveries in the Tsan Yuk Hospital. In this same period 65 cases of compound presentation were encountered,