PACHYDERMOPERIOSTOSIS

A REVIEW OF LITERATURE AND REPORT ON FOUR CASES

BY

K. SHAWARBY, M.B., M.R.C.P.Ed.

AND

M. SALAH IBRAHIM, M.B., M.R.C.P.Ed.

From the Department of Medicine, Ein-Shams University, Cairo

Pachydermoperiostosis is a disease characterized by certain changes in the skin and bones that closely resemble pulmonary hypertrophic osteoarthropathy. In pachydermoperiostosis, however, no causative factors such as pulmonary, cardiac, or hepatic disorders have been demonstrated.

The disease was first described in two young brothers by Friedreich in 1868. Some 60 cases have been reported since, mostly in the French literature, but the disease was established as a clinical entity only within the last twenty years (Vague, 1948, 1950; Findlay and Oosthuizen, 1951; Angel, 1957).

Clinical Features

Males are predominantly affected and changes usually set in shortly after puberty. The disease often occurs in brothers; all these patients appear to be infertile.

Skin Changes.—Thickening of the skin occurs over the face, forehead, scalp, hands, and feet. The face is drawn into thick folds, giving it a creased appearance. The most prominent of these folds are on the forehead, cheeks, and nasolabial folds, a condition known as *cutis verticis gyrata*. The eyelids are often thickened. The skin is greasy and may show changes due to acne. Histological examination of the skin shows increased thickness of the epidermis, with hypoplasia of the sweat and sebaceous glands and histiocytic infiltration of the corium.

Bone Changes.—The bones, especially those of the distal parts of the limbs, are broadened without being increased in length. This may give rise to marked thickening of the wrists, lower parts of the legs, and ankles, as well as to increased size of hands and feet. The nails may be thickened and curved, with severe clubbing of the fingers and toes. Effusions into the knees and ankles, which may produce pronounced swelling of these joints, are often present. A bone biopsy by Leinwand and Duryee (1943) showed foci of plasma cells in the paraperiosteal tissues. Radiological studies show cortical thickening and irregular cortical outgrowths due to deposition of periosteal new bone on the diaphyses of long bones, particularly of the more distal parts. It is very rare for the carpus, tarsus, vertebrae, or skull to be involved. No changes occur in the articular surfaces.

Symptoms.—Patients complain chiefly of heavy perspiration over the hands and feet and sometimes over the face, clumsiness in the use of the extremities, and pain in the limbs, especially when joints are involved.

Course and Prognosis.—These abnormal processes usually progress slowly and painlessly for several years. Lasting and natural arrest may then occur, but after a

variable interval an increase in bone production may begin again, and may develop towards a universal hyperostosis of the skeleton with ossification of ligaments and fusion of certain joints. Joint fusion is seen especially in the carpus, tarsus, and vertebral column. Eventually this may lead to compression of the spinal cord and nerve roots. The prognosis as regards life is excellent; as regards function it depends on the degree of affection of the bones and joints.

Differential Diagnosis

Pachydermoperiostosis has to be differentiated from the following conditions:

Hypertrophic Pulmonary Osteoarthropathy.—There is close resemblance, due to the presence of enlarged hands and feet with marked clubbing and swollen joints. It can be distinguished by the following points: (a) the disease starts later in life than pachydermoperiostosis and is progressive; (b) pain in the joints is often a prominent symptom; (c) the skin is usually lightly involved; and (d) an underlying cause is always found in the lungs, heart, etc.

Acromegaly.—Confusion may arise as a result of the enlargement of the hands and feet, and hypertrophy of skin. The mandible, nose, supraorbital ridges, and tongue are, however, enlarged in acromegaly. The sella turcica is enlarged in most cases as a result of a pituitary adenoma which may give rise to characteristic defects in the visual field. The air sinuses are enlarged and the terminal phalanges tufted. Inorganic serum phosphorus is raised during the active stage.

Thyroid Acropathy.—This condition occurs in hyperthyroid patients who become hypothyroid as a result of surgical or medical treatment. The distal parts of the limbs may become enlarged, and clubbing of the fingers and toes may take place. Radiological examination may show subperiosteal new formation in the bones of the hands. Malignant exophthalmos and possibly pretibial myxoedema are present.

Pachydermoperiostosis has also been mistaken on occasion for osteitis deformans, syphilitic periostitis, and leprosy.

Case 1

A single man aged 27 presented with swelling of the knees, ankles, and feet, which had started nine years previously and was getting worse. Pain in the legs had been felt for five years on walking. He had first noticed the development of prominent skin folds of the face at the age of 20. He also complained of profuse sweating of the hands and feet and heaviness of the eyelids. His brother was also affected (see Case 2).

On examination his height was 170 cm., upper measurement 82 cm., lower measurement 88 cm., span 172 cm., and weight 56 kg. He looked timid and older than his age. The skin of the face, forehead, and anterior part of the scalp was thickened and greasy and thrown into deep folds (Fig. 1). The nasolabial folds were greatly exaggerated, the nose was big, the eyelids were thickened, and the palpebral fissures were narrow. He had an adherent leucoma in the right eye. The skin of the peripheral parts of the limbs was also thickened. The skull, tongue, and jaw were normal in size. He had a moustache and a fine beard. The pubic hair was feminine in distribution; the axillary hair was normal. Testes were normal.

There was huge swelling of both knees, with massive effusions. The ankles were swollen and the feet enlarged. The bones of the limbs were thickened, especially in the legs. The hands and fingers were thick and broad (Fig. 2), with drumstick clubbing of the fingers and toes. The thyroid

gland was slightly enlarged and nodular. The field of vision of the sound eye was normal. The chest and cardiovascular system were normal. The spleen was just palpable (this had not been noticed when he was examined three years previously). The lymph nodes were not enlarged.

Investigations.—Blood: Hb 80%; red cells 3,900,000/c.mm. (hypochromic); white cells normal. B.M.R. -11%.

FIG. 1.—Case 1. Photograph showing typical and prominent folds of skin on forehead, cheeks, and nasolabial folds (cutis verticis gyrata).

FIG. 2.—Case 1. Notice enlarged wrist joints and clubbing of fingers.

FIG. 3.—Case 1. Cross-section of skin of face. The epidermis is thickened, the sebaceous and sweat glands are large, and there is infiltration with inflammatory cells.

^{131}I uptake: 3 hours 5.8%, 24 hours 27.5%. Serum inorganic phosphorus 3.5 mg./100 ml. Serum alkaline phosphatase 8 K.A. units. Serum cholesterol 150 mg./100 ml. Blood-sugar curve normal. Liver-function tests (including bromsulphthalein test) normal. W.R. negative. Skin biopsy: Skin was rich in sebaceous glands and hair follicles; few small foci of chronic inflammatory cells were present in the dermis (Fig. 3). A biopsy of the synovial membrane of the knees was refused.

X-Ray Examination.—Chest and heart: No abnormality detected. Lower limbs: huge effusions in both knee-joints; exostoses of lower ends of both femora (Fig. 4); periosteal reaction in tibiae, fibulae, metatarsals, proximal phalanges (Fig. 5), and lower ends of femora. Upper limbs: periosteal reaction in radius, ulna, metacarpals, and proximal two rows of phalanges. Vertebral column normal. Skull: normal sella turcica; the frontal air sinuses were not developed.

Case 2

A brother of the previous patient, a single man aged 23, presented with wrinkling of the skin of the face (Fig. 6), aching pains in the legs on standing and walking, and excessive sweating of the hands and feet which had been noticed for four years.

On examination his height was 171 cm., upper measurement 82 cm., lower measurement 89 cm., and span 184 cm.

The face showed prominent skin folds of the forehead and nasolabial folds. The sebaceous secretion was excessive and acne was present. The nose was big. The thyroid gland was slightly enlarged and nodular. Chest was pigeon-shaped with slight kyphosis. The feet were enlarged, and the ankles were more markedly swollen than the knees, with effusion. Moderate clubbing of the fingers and toes was present. Both fundi and fields of vision were normal. The cardiovascular system and abdomen showed no abnormality.

The laboratory investigations (same as those of previous case) gave normal values. X-ray examination of limbs showed periosteal reaction in forearms, metacarpals, and proximal two rows of phalanges; the legs and feet showed less prominent reaction. X-ray examination of the

FIG. 4.—Case 1. X-ray film of left knee-joint showing evidence of effusion, periosteal reaction, and thickening of soft tissues.

FIG. 5.—Case 1. X-ray film of left hand showing periosteal changes.

chest and skull revealed no abnormality. Skin biopsy showed changes similar to those in Case 1.

Case 3

This patient was a single man aged 21. About the age of 15 years—that is, one year after puberty—the disease started with painless swelling of ankles and feet. He easily became tired, sweated excessively, and movements of the hands were clumsy. Skin changes appeared three years later, and were earliest and most prominent on the forehead. Seborrhoea and acne were very pronounced. The patient was psychologically disturbed; he had to quit school for some time and entertained suicidal ideas. The B.M.R. was done in another hospital two years before admission, and was found to be -25% . Desiccated thyroid was then given, but he showed no improvement. His grandmother developed acromegaly at the age of 55 and died at the age of 70.

On examination his face was seen to be prematurely aged. The skin of the face was thickened, greasy, and thrown into very prominent folds. These folds were equally marked on the forehead, scalp, and cheeks; the nasolabial folds were greatly exaggerated. The eyelids were very thick and the palpebral fissures narrowed (Fig. 7). His nose was large, shiny, and bulbous. Neither the jaw nor the tongue

was enlarged. His height was 175 cm., upper measurement 86 cm., lower measurement 89 cm. The size of the hands and feet was greatly increased without clubbing of the fingers or toes. The wrists, the lower third of the forearms, and the legs up to mid-thigh level were thickened. The ankles and knees were swollen; there was a moderate effusion in the right knee-joint. There were no abnormalities in the chest or cardiovascular system. The thyroid gland was not palpable, and the visual fields were found to be normal.

The laboratory investigations (same as those in the previous two cases) were normal. B.M.R. $+15\%$. X-ray examination showed a normal sella turcica and normal lower jaw, and subperiosteal deposition of new bone involving the metacarpals, proximal two rows of phalanges, and lower third of

radius and ulna. The lower limbs showed similar changes up to the lower half of the femur.

Skin biopsy showed changes similar to those in the previous two cases.

Case 4

A married man aged 43, with two children aged 5 and 7, came under observation while in hospital visiting one of his relatives. He suffered from no symptoms, but admitted that his fingers had been noted to be abnormal by a doctor several years before. He had one brother and three sisters; all appeared normal. His children also showed no abnormality.

On examination his height was 167 cm., upper measurement 80 cm., lower measurement 87 cm., and weight 60 kg. The skin of the face was thickened and greasy, with marked exaggeration of the nasolabial folds. The hands and fingers were larger than normal. Marked clubbing of the fingers and toes was present. There was no abnormality in the cardiovascular system, chest, or abdomen. The joints showed no swelling. The thyroid gland was not palpable.

The laboratory investigations (same as those of the previous cases) were within normal limits. Plasma sodium 132 mEq/l.

X-ray examination showed a normal chest and skull, and slight periosteal reaction in the metacarpals and phalanges. Skin biopsy showed changes similar to those in previous cases, but with little infiltration with histiocytes.

Discussion

The fact that the disease is familial in over a quarter of the cases (Vague, 1948, 1950) makes the possibility of an underlying genetic disorder very likely. De Seze and Jurmand (1950) suggested that inheritance is transmitted by a recessive or incompletely dominant gene. They also observed that both pachydermoperiostosis and pulmonary osteoarthropathy may affect different members of the same family, and concluded that both conditions may be predisposed to by a common pathogenic gene.

Recently, low serum-sodium levels with normal excretion of sodium were reported in patients with pachydermoperiostosis (Törnblom *et al.*, 1959). This hyponatraemia with normal conservation of sodium (unlike adrenal cortical insufficiency) seems to agree with that described in bronchogenic carcinoma and advanced tuberculosis in which an impairment of the active energy-consuming process of maintaining the difference in the concentration of extracellular and intracellular sodium was suggested. A similar congenital impairment of such a process might be present in pachydermoperiostosis (Törnblom *et al.*, 1959).

Our first two patients represent a complete picture of pachydermoperiostosis, and being brothers they illustrate the genetic factor of the disease. Incomplete forms of the disease may, however, occur; the third patient showed typical skin and bone changes, but did not have clubbing of the fingers.

On the other hand, there are certain points which raise suspicion that pachydermoperiostosis may result from an endocrine disorder. First, a disorder of the adenohypophysis might be suspected as a result of overgrowth of the extremities and skin, similar to acromegaly. Also, clubbing and periosteal changes (similar to those of pachydermoperiostosis) observed in thyroid acropathy are thought to arise from a disorder of the adenohypophysis. Fried (1943) reported in four cases of pachydermoperiostosis features of

FIG. 6.—Cases 1 and 2. The two brothers. Notice marked enlargement of both knee-joints of elder brother (Case 1).

FIG. 7.—Case 3. Skin of face and forehead is thickened and thrown into prominent folds. Notice thickened eyelids and narrow palpebral fissures.

acromegaly, including prognathism and macroglossia. Biochemical investigations were not undertaken in these cases, but necropsy revealed enlargement of the pituitary in two cases, and adenomata of the adrenal cortex and thyroid also in two cases. Secondly, a disorder of the thyroid might be suspected. Cases 1 and 2 had nodular enlargement of the thyroid; Cases 1 and 3 had low basal metabolic rates. Case 3 received thyroid treatment for two years with no apparent improvement. It would, however, be tempting to assume a disturbed target-cell sensitivity in the acral tissues, especially skin and bones, to normally secreted hormones. Recent work on the aetiology of hypometabolism may provide evidence to confirm this possibility (Kurland *et al.*, 1955).

A different mechanism which may result from opening up of the arteriovenous anastomoses in the distal parts of the extremities is suggested from the work of Flavell (1956) and Huckstep and Bodkin (1958). They demonstrated that section of the vagus nerve below the aortic arch brought about relief of the arthralgia, the oedema, and the acral enlargement in cases of inoperable lung neoplasms complicated by severe osteoarthropathy.

Summary

Four cases of the syndrome known as pachydermoperiostosis are recorded. The main features of this syndrome consist of: (1) thickening of the skin, especially over the face and scalp, which becomes drawn into thick folds; (2) marked clubbing of the fingers and toes; (3) broadening of the bones at the distal parts of the limbs with irregular periosteal new-bone formation; (4) effusions into joints, especially knees and ankles.

Two of the patients are brothers and represent a complete picture of the syndrome. The remaining two show incomplete forms. In Case 3 there is no clubbing of the fingers, although he has all the other features. Swelling of the joints is absent in Case 4. This patient, being married with two children, seems to provide an exception to the general belief that these patients are sterile.

The aetiology is unknown. The condition appears to be genetic; several theories explaining the possible mechanism are discussed.

We thank Professor P. Ghalioungui, Chief of the Department of Medicine, Ein-Shams University Hospital, for suggesting that the paper should be written and for his continued interest during its preparation. Thanks are due to Mr. H. Munib for reading the manuscript.

REFERENCES

- Angel, J. H. (1957). *Brit. med. J.*, **2**, 789.
 De Seze, S., and Jurmand, S.-H. (1950). *Bull. Soc. méd. Hôp. Paris*, **66**, 860.
 Findlay, G. H., and Oosthuizen, W. J. (1951). *S. Afr. med. J.*, **25**, 747.
 Flavell, G. (1956). *Lancet*, **1**, 260.
 Fried, B. M. (1943). *Arch. intern. Med.*, **72**, 565.
 Friedrich, N. (1868). *Virchows Arch. path. Anat.*, **43**, 83. Cited by Findlay and Oosthuizen (1951).
 Huckstep, R. L., and Bodkin, P. E. (1958). *Lancet*, **2**, 343.
 Kurland, G. S., Hamolsky, M. W., and Freedberg, A. S. (1955). *J. clin. Endocr.*, **15**, 1354.
 Leinwand, I., and Duryee, A. W. (1943). *Ann. intern. Med.*, **19**, 1018.
 Törnblom, N., Malers, E., and Wallenius, G. (1959). *Acta med. scand.*, **164**, 325.
 Vague, J. (1948). *Rev. Rhum.*, **15**, 201.
 — (1950). *Ann. méd.*, **51**, 152.

MUCORMYCOSIS OF HEAD AND NECK STRUCTURES

A CASE WITH SURVIVAL

BY

H. BANK, M.B., Ch.B.

S. SHIBOLET, M.D.

T. GILAT, M.D.

G. ALTMANN, M.S.

AND

H. HELLER, M.D.

*Department of Medicine and Department of Bacteriology,
Tel Hashomer Government Hospital, Israel*

It is only during the past few years that reports of disease in man caused by the fungus *Mucor* have begun to multiply. Since the report by Graham (1890) only two reports of visceral involvement by this fungus have been published in the British literature (Kurrein, 1954; Muresan, 1960). That the condition is not very rare is shown by the report of Neame and Rayner (1960), who found mucormycosis in 0.68% of all necropsies in a Durban hospital during a period of 10 months. Mucormycosis refers to infection by fungi of the order Mucorales, class Phycomycetes. These are ubiquitous saprophytes and are found on decaying vegetable matter, in soil, or as bread moulds (Conant *et al.*, 1954). In man the disease has usually been due to one of three genera of the Mucorales: *Rhizopus*, *Mucor*, or *Absidia*. The literature has been reviewed by a number of authors (Hutter, 1959; McBride *et al.*, 1960; Neame and Rayner, 1960).

The following case diagnosed during life appears to be the ninth reported case of cerebral mucormycosis with survival (Hutter, 1959; Dwyer and Changus, 1958).

Case History

The patient was a 60-year-old Jew, born in Iraq. His illness started one week before admission, with fever, pains in the right frontal and auricular region, and rhinitis. He was treated with antibiotics and admitted to hospital because of the appearance of chemosis and marked oedema of both eyelids on the right.

On examination an acute ethmoiditis was found and external ethmoidotomy was at once performed. A small quantity of pus was evacuated and the ethmoidal sinus drained. Fundoscopy at this stage was normal. On the second post-operative day the patient became somnolent, and a left hemiplegia and right internal and external ophthalmoplegia with proptosis became apparent. He was stuporose, reacting only to forceful stimuli. There was neck stiffness. His temperature was 38° C., pulse 88, blood-pressure 130/80.

The right eye was bulging forward and outward. There was marked swelling of the conjunctiva, eyelids, and surrounding tissues (Fig. 1). Many small pustules were seen on the skin surrounding the eye. The base of the drainage wound was grey and necrotic. There was a purulent retranasal discharge. The left eye was normal but deviated to the right. Carotid pulsation was present bilaterally. No arterial bruits were noted. The rest of the physical examination was negative.

Laboratory Findings.—Haemoglobin 13.6 g./100 ml.; leucocytes 32,500, with a marked shift to the left. Urine: acetone+, sugar 2.8%, albumin+, 2-8 leucocytes per field.