Fibrous Dysplasia of Bone with Skeletal Lipoid Granulomatosis

Report of a Case with Necropsy

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This case is reported on account of the unusual combination of unilateral fibrous dysplasia of bone with lipoid granulomatosis. The disorder was also complicated by a neurological condition in which there were plaques of demyelination in the central nervous system, an association not so far reported.

CASE REPORT

The patient, aged fifty, had been healthy in childhood; at school she had been considered tall for her age but she ceased to grow after the age of fourteen. Menstruation started at the age of fifteen years and was normal. She married at nineteen, and had one son, who is healthy. She sustained no fractures. At the age of thirty-one years she complained of frontal headaches and vomiting; at that time the only abnormality then noted was “bossing” of the right frontal bone. When she was aged thirty-seven, radiography of the right femur, because of lumbar pain and pain and tenderness in the right thigh, suggested Paget’s disease. At the age of forty-two, radiography of the right tibia because of pain and bowing, revealed changes there also. No biochemical abnormality was found. A biopsy of the femur showed “interstitial fibrosis.” The neck was explored and the left upper parathyroid gland removed. Its histology was normal.

At the age of forty-eight years, she was admitted to the Royal Victoria Hospital, Belfast. Bossing of the right frontal bone had increased and there was proptosis of the right eye. Patches of light brown pigmentation were noted in the right temporal region and on the left side of the chin, and smaller patches were present on the back of the right hand and on the front of the legs below the knees. Radiographs of the skeleton (Fig. 1) showed that the following bones were affected: right frontal bone, base and vault of skull, right femur, right tibia and right fifth metacarpal bone. The serum calcium, inorganic serum phosphorus and alkaline phosphatase levels were repeatedly within normal limits. A tentative diagnosis of fibrous dysplasia of bone was made.

There was little change in the skeletal condition until her death, but when she was fifty the cutaneous pigmentation had disappeared, except from the face. She continued to be distressed by severe generalised pains.

The clinical picture was complicated from the age of forty-six onwards by a neurological condition diagnosed as disseminated sclerosis. This was brought to notice when she was admitted to hospital on account of unconsciousness, which lasted several hours and was followed by spastic paraplegia which persisted. Two years later the left arm showed paresis,
and she complained of transient blurring of vision although nothing was found objectively. Later the same year she suffered severe abdominal pain and vomiting. A right-sided Horner’s syndrome appeared temporarily. There was stress incontinence of urine, with frequency and occasional precipitancy.

A year before her death the legs were contracted in flexion. General wasting of the left hand had developed, and all modalities of sensation were slightly involved in the left arm. Her general condition deteriorated steadily and she died in uraemia at the age of fifty.

**Post-mortem-examination**—The body, of moderate nutrition, showed deformities: a large bony swelling within the right frontal bone 6 centimetres in diameter, causing slight proptosis of the right eye; prominence of the right maxilla; bowing of the right tibia; and flexion contractures of both lower limbs. Slight brown pigmentation in two fairly well defined areas was seen over the right cheek and over the left side of the chin. *Viscera*—No lesions were seen in the thoracic abdominal viscera, except in the lungs which were oedematous and congested, the kidneys which showed marked changes of pyelonephritis, and the bladder which showed a chronic cystitis. *Brain and cord*—The meninges were not thickened and there was no evidence of cerebral swelling. After fixation, brain and cord were sectioned at 5-millimetre intervals. Within the brain no lesion was visible until the hind-brain was reached. In the vicinity of the roof of the fourth ventricle a firm grey plaque was seen within the cerebellum, situated on the left side and occupying the posterior half of the dentate nucleus and adjacent white matter. There were no other plaques in the cerebral hemispheres or in the brain stem. Within the cord, numerous plaques involved all columns at different levels, and were most marked in the cervical region.

**Skeletal system**—Right frontal bone: On section of the tumour the tissues consisted of extremely hard granular and bony material. Tiny spicules of bone could be seen enmeshed in the white granular material, which had one or two slightly darker areas scattered in it. Right tibia and right femur: On section the cortex was irregularly thinned. The medulla had been entirely replaced by firm white tissue, which contained numerous bony-hard spicules. Within it there were several cysts measuring 1 to 2 centimetres in diameter and containing bright green or brown mucoid material. Vertebral bodies: The lower thoracic and upper lumbar vertebral bodies were normal on section. The marrow was the usual deep red colour.

**Histological examination. Kidneys and bladder**—The pyelonephritis and cystitis were confirmed. The remaining thoracic and abdominal *viscera* presented normal appearances.

**Brain and spinal cord**—Sections from the brain and cord at different levels were stained by the usual techniques. The plaques seen macroscopically consisted of well demarcated areas of complete demyelinisation with preservation of ganglion cells and axis cylinders. These areas showed a marked gliosis. Fat was absent. Some of the plaques showed a peculiar predilection for the posterior horns, and at some levels were confined to these (Fig. 2). In the cervical region the plaques involved the anterior horns. Here there was some reduction in the number of ganglion cells; those remaining were normal. Gliosis was striking, and actively dividing astrocytes were present in the anterior horns. There was slight evidence of ascending and descending degeneration in the appropriate columns. No lipoid could be detected in the sections studied, in cord or brain. **Thyroid, adrenal, pituitary**—No changes were observed.

**Bone**—Numerous areas of affected and unaffected bone were studied. Variations of the same pathological process were seen in the tibia, the femur and the right frontal bone. The medulla of the bones was replaced by a peculiar tissue which in many fields consisted of masses of foam cells intermingling with relatively cellular fibrous tissue. These foam cells had a reticulated cytoplasm and a small dark nucleus, usually placed eccentrically (Fig. 3). Occasional giant forms with several nuclei were seen. Scattered amongst this tissue were groups of eosinophils and lymphocytes. Such fields merged gradually into others where intervening strands of collagen were more prominent, fibrocytic nuclei were scarcer and narrower, and foam cells were no longer identifiable (Fig. 4). But in these areas lipoid was relatively abundant.
in frozen sections, and was mostly extracellular (Fig. 5). It was identified here, and in sites of foam cell formation as a mixture of cholesterol and cholesterol esters by the Nile blue sulphate, Liebermann-Burchard and digitonine reactions. In some fields, new bone formation was entirely lacking. It was more common to find bony trabeculae, however, both where foam cells were obvious and in the large areas of marrow fibrosis. These trabeculae were studded with tiny globules of calcium salts, or were more homogeneous. In either case
the interweaving collagen fibres on which the bone was formed could be made out (Fig. 4). Few osteoblasts lined these trabeculae. Occasional trabeculae of lamellar bone could be seen, usually near the cortical compact bone, and were interpreted as surviving trabeculae. In only one or two places was there osteoclastic activity with erosion of lamellar bone trabeculae. There were no giant-cell tumours. Sometimes osteoid seams were present along the margins of the fibre bone trabeculae, and in some areas, again near the cortex, osteoid was deposited by itself in small adjacent pavement-like islands. Foam-cell formation, in sections stained with haematoxylin and eosin, was present in about half of the affected marrow. In the fibrotic marrow calcium salts were irregularly distributed in the form of fine granules and clumps. They were most noticeable in the walls of the large cysts, which contained a homogeneous acidophilic colloid substance. The cysts were bounded by a narrow rim of compressed fibrous tissue in some instances, and in others merged gradually into the surrounding fibrous tissue. They were ascribed to focal degeneration. No foci of recent haemorrhage were encountered, although a few granules of haemosiderin were seen in one area. Vessels were sparse, and were thin-walled sinusoidal capillaries. They were more frequently seen in the foam-cell granulomatous areas.

The bone cortex was altered by the granulomatous process in the medulla. It was narrowed in many places, and its Haversian canals were widely dilated. They contained either normal fatty marrow or were filled by a fibrous tissue with a tendency to whorl and in which the fibrocytic nuclei were plumper than anywhere else. This tissue was practically free from foam cells. No islands of cartilage formation were encountered.

DISCUSSION

This case shows the characteristics of fibrous dysplasia of bone (Lichtenstein and Jaffe 1942). Pigmentation was present, but not sexual precocity, so that it cannot be labelled the rare Albright’s syndrome (Albright et al. 1937), although there was possibly evidence of accelerated skeletal development (Önne 1951). The disorder is generally considered developmental, because of the predominantly unilateral distribution of the bony lesions, the occasional pigmentation, the usual early age of onset and the not uncommon association with congenital anomalies. Ten cases with such an association have been discovered in the literature by Vines (1952) and in addition a case with congenital cataracts has been reported by Meyersohn and Grek (1951). Transmission to a daughter has been reported once (Hibbs and Rush 1962). Endocrine disturbance, when present, is considered to be secondary, perhaps to involvement of the pituitary fossa.

This patient did not show any sign of bony disease until the age of thirty-one, when a bossing of the right frontal bone was noted, but the age of onset cannot be ascertained because often the affection is symptomless for years and may be discovered accidentally.

The histological findings in the skeleton were in many respects identical with those of fibrous dysplasia. In affected areas of bone only, there was thinning of the cortex, with erosion, replacement of the cancellous marrow by a proliferating fibrous tissue, which formed numerous trabeculae of fibre bone and in which cysts containing gelatinous material were found. No islands of cartilage, such as are occasionally present, were discovered. The one uncommon feature was the ubiquitous presence of cholesterol and its esters within large sheets of well formed foam cells, or in the interstices of the mature or old fibrous tissue where it could only be detected on special staining. Foam cells have been noted many times in this disease, but mostly in small islands. Dockerty et al. (1945) stated that they never occur in the abundance in which they may be present in “xanthoma.” Russell and Chandler (1950) considered that they are of no significance. Jaffe (1945), Pritchard (1951) and others held that they represent a reaction to haemorrhage and degeneration.

The explanation of the presence of the lipid, extracellular and intracellular, in our case is not easy. It is obviously not the result of a focal reaction to haemorrhage or
degeneration. Dominating the histological picture in all areas studied, it can scarcely be a mere secondary infiltration. The histological picture suggests the reverse: there is a transition from areas where the fibrous tissue is young and active and foam cells are abundant, to other areas of relatively acellular collagenous fibrous tissue. Here foam cells are no longer found but lipoid is present in the interstices of the tissue, where it can be detected only by special staining. It becomes apparent that we are dealing with a condition histologically akin to lipoid granulomatosis of bone, the osseous form of Hand-Schüller-Christian disease.

Christian considered the syndrome of defects of membranous bones, exophthalmos and diabetes insipidus to be due to dyspituitarism, but later authors such as Thompson, Keegan and Dunn (1925) ascribed the endocrine features of the disease to pressure by altered bone on the hypothalamic region. There is a parallel here with Albright’s syndrome: in cases showing endocrine disturbance there is usually a marked change in the bones of the skull base (Önne 1951). The present tendency is to consider the bony changes in Hand-Schüller-Christian disease to be paramount, and to consist of a granulomatous process involving the reticulo-endothelial system. There is a proliferation of histiocytic elements, with infiltration by lymphocytes and eosinophil cells. In a later phase, these histiocytes develop into foam cells containing cholesterol and its esters, and in the final stages there is gradual disappearance of foam cells with development of fibrous tissue. This was seen, for example, in the first case coming to necropsy (Thompson et al. 1925). The arguments that the condition is not a primary disturbance in cholesterol metabolism, as suggested by Rowland (1928), are now well known (Snapper 1945, Jaffe and Lichtenstein 1944, Wallgren 1940) and need not be repeated. In our case the fibrous tissue showed distinct metaplasia to irregular, poorly formed fibre-bone trabeculae, a process which has been stated not to occur in lipoid granulomatosis. According to Robb-Smith (1942), new bone is rare in Hand-Schüller-Christian disease, and when found is lamellar bone. It must be remembered that many patients with Hand-Schüller-Christian disease die at an early age, and there may not be time for such a process, which represents an attempt at healing of the lesion, to occur. It has however been described in older patients. In one example, a man aged fifty, coming to necropsy and minutely described by Heine (1935), fibre-bone formation as well as lamellar bone was a prominent feature in the oldest lesions. New bone, lamellar and fibre, occurred in both of Chester’s cases (1930). Therefore, metaplasia of the fibrous tissue to bone, fibrous and lamellar, is quite consistent with lipoid granulomatosis.

The histological features of this case are thus in keeping with the diagnosis of skeletal lipoid granulomatosis, and yet it presents the cutaneous and skeletal features of fibrous dysplasia with cutaneous pigmentation.

The existence of fibrous dysplasia of bones and the rarer, complete Albright’s syndrome as a separate entity cannot be questioned. A very large number of cases exists whose pathological diagnosis rests on adequate biopsy material, even though detailed necropsy reports are scarce (Sternberg and Joseph 1942, Uehlinger 1940, Jervis and Schein 1951). In most cases foam cells have been seen only in small islands or have not been found, even on the rare occasions when looked for by specific staining methods (Valls et al. 1950). Snapper (1943) was formerly of the opinion that such cases represent a burnt-out lipoid granulomatosis, but the evidence that fibrous dysplasia of bone is a dysplasia separates the two conditions. Nevertheless there does appear to be a small group of cases of fibrous dysplasia in which foam-cell formation is an integral part of the disease process, among them Snapper’s two cases (1949), and that reported by Sánchez-Lucas and Castells Freixà (1949). The latter authors viewed their case as a combination of fibrous dysplasia and xanthomatosis. We consider that it is only possible to say at present that a small proportion of cases of fibrous dysplasia exists in which the skeletal lesion takes the form of a lipoid granulomatosis. Further studies of necropsy and biopsy material, bearing in mind that lipoid may be missed in haematoxylin and eosin sections, may increase this proportion, and a closer relationship may
be discovered between lipoid granulomatosis on the one hand and fibrous dysplasia of bones on the other. The diagnosis of fibrous dysplasia has perhaps been too freely entertained, and many cases of the monostotic form, as Schlumberger (1946) observed, should be ascribed to an atypical reaction to trauma.

The neurological disorder which complicated our case is of some interest and adds support, however slight, to the concept of lipoid granulomatosis. The morbid anatomical picture, as it stands at present, is indistinguishable from disseminated sclerosis, and in fact the case is similar to those described in the older patients, in which anterior horn cell destruction was not infrequent (Friedman and Davison 1945). However, in an undoubted case of Hand-Schüller-Christian disease, Heine (1935) discovered numerous minute foci of demyelinisation and gliosis, with conservation of axis cylinders and nerve cells, scattered throughout the brain. He considered that they might well represent the healed stage of lipoid granulomata in the brain. Such had been seen in another case reported by Chiari (1931) where actual foam cell deposits were found in brain substance as well as plaques of demyelinisation. Plaques were also seen in Davison's case (1933), and lipoid infiltrations in the neuraxis were described by van Bogaert, Scherer and Epstein (1937), Guillain, Bertrand and Godet-Guillain (1942), and Weidman and Schaffer (1937). Thus lipoid or lipo-granulomatous infiltrates may occur within the neuraxis and have apparently given rise to plaques of demyelinisation. Such a derivation for the plaques in our case is an interesting probability, though far from proven.

No such focal demyelinisation has been described in fibrous dysplasia of bone. In the case with cerebral symptoms reported by Jervis and Schein (1951) the findings were of an entirely different character, suggesting a developmental origin. Giant ganglion cells were found, and a general deficiency in nerve cells in grey matter without any glial reaction. Although there were no giant glial cells or glial nodes, the condition was held to be akin to tuberose sclerosis.

**SUMMARY**

1. A case of fibrous dysplasia in a woman aged fifty, with unilateral skeletal lesions, cutaneous pigmentation and possibly accelerated skeletal growth, is described.
2. At necropsy, the bony changes were found to be complicated by many of the changes of lipoid granulomatosis. Disseminated plaques of demyelinisation were found in the central nervous system.
3. The implications of the case are discussed.

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