

Albright's Syndrome with Hypophosphatemic Rickets and Hyperthyroidism

- A case report -

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In this abstract we report a case of Albright's syndrome associated with hypophosphatemic rickets and hyperthyroidism in a six-year-old girl. She had suffered from repeated fractures of her long bones owing to multiple locations of radiolucent areas and generalized skeletal demineralization. The biopsy in the lucent area revealed histologic appearance of fibrous dysplasia.

Key Words : Albright's syndrome, hypophosphatemic rickets, hyperthyroidism

The mechanism of various endocrine disturbances in Albright's syndrome is not yet established. Dent and Gertner (1976) has suggested that the pathogenesis of hypophosphatemic rickets in these cases is analogous to the syndrome of "tumor rickets". Linovitz et al (1976) and Stanbury (1972) have discussed the resolution of hypophosphatemic rickets after complete removal of the associated tumor, and this was thought to be a potentially curable form of rickets. Fibrous dysplasia, which occurs singly, has also been reportedly resolved following surgical removal. However, polyostotic fibrous dysplasia of Albright's syndrome is difficult to surgically correct; therefore, resolution of hypophosphatemic rickets is difficult to expect. We are reporting an additional case of Albright's syndrome with hypophosphatemic rickets and hyperthyroidism.

CASE REPORT

A six-year-old girl sustained a slipping-down injury of her right lower extremity and was first seen at

Severance hospital in April 1989. She had been relatively good health up to three ago when she began to suffer from easy fatigue, generalized bone pain and a mild degree of weakness. She has managed to live without specific treatment by her parents.

On clinical examination, there was painful swelling with false motion of her right thigh. She had irregular patchy dark-brownish pigmentation of the skin over the face, abdomen, back and both lower extremities (Fig. 1). Mild degree of pectus excavatum deformity of chest wall and bowleg appearance was noted. There was engorgement of both breasts (Tanner stage II), but pubic hair was not present. Her initial blood pressure was 160/90. Neurological examination was negative. There was no familial history of rickets. Her height was in the 75 percentile range and her weight was in the 25 percentile range.

Radiographs revealed a fracture of the mid-portion of her right femur. There was generalized skeletal demineralization along with relative fraying and irregularities of metaphysis of the long bones. There were also expanded lucent areas in the proximal and the distal portion of the right femur and in the proximal portion of the left fibula with thick sclerotic margins (Fig. 2). The skull showed thickening of the basal, frontal and occipital bones.

Technetium-99m diphosphonate bone scan showed diffuse increased uptake in the skull bone

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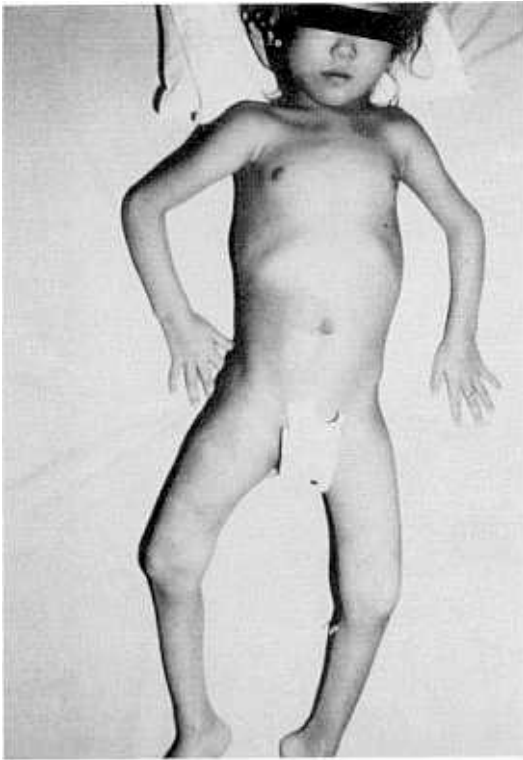


Fig. 1. Photographs showing large café au lait spot with irregular margins on the face and right abdomen in a six-year-old girl.



Fig. 2. Radiograph showing generalized demineralization and pathologic fracture on mid-portion of right femur. Note expanded lucent areas with sclerotic margins on the proximal and distal portion of it.

Table 1. Result of biochemical investigation

Investigation(serum)	Result	Normal	Value
Calcium	9.5 mg/dl	8.8-10.8	mg/dl
Phosphorus	3.3 mg/dl	4.5-6.5	mg/dl
Alkalinephosphatase	760 IU/l	60-300	IU/l
LH	<1 mIU/ml	2.0-15.4	mIU/l
FSH	<1 mIU/ml	1.9-8.5	mIU/l
Estradiol(E2)	<10 Pg/ml	30-400	pg/ml
Testosterone	0.23 ng/ml	0.2-0.8	ng/ml
T3	382.73 ng/dl	80-220	ng/dl
T4	18.97 ug/dl	5-13	ug/dl
TSH	<0.01 uIU/ml	0-7	uIU/ml
VMA	5.3 mg/day	2-10	mg/day
Epinephrine	311 pg/ml	0-375	pg/ml

and maxilla, right clavicle and right proximal femur. The results of biochemical investigation are shown

Table 2. Gonadotropin response to a single intravenous bolus of LHRH(40 IU)

	LH(mIU/ml)	FSH(mIU/ml)
initial		
after 30 min		
after 60 min		
after 90 min		
after 120 min		

in Table 1. Serum phosphorus level was low, ranging from 2.8 to 3.8 milligrams per deciliter. In view of the possibility of abnormal hypothalamic-pituitary function in fibrous dysplasia, endocrine assessment was carried out. She had normal pre-pubertal levels of LH and FSH, showed no unusual response of LH level to LHRH stimulation (Table 2). Levels of both the thyroxine and triiodothyronine was elevated,

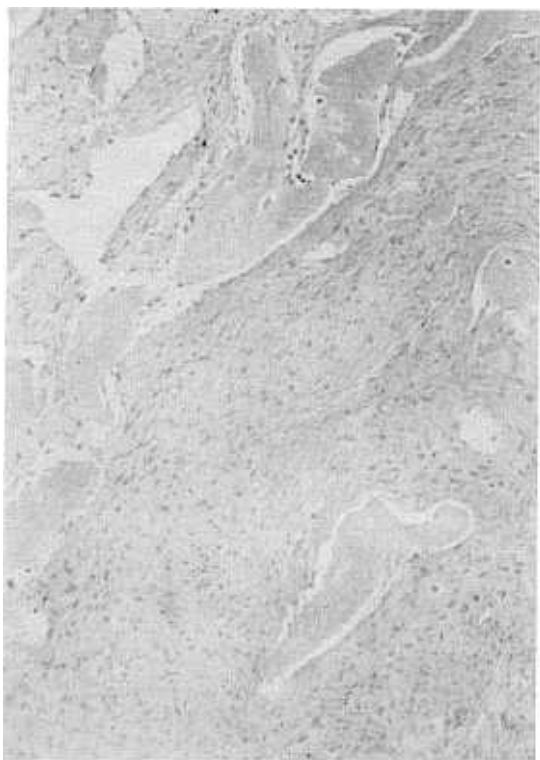


Fig. 3. Biopsy specimen showing classic fibrous dysplasia with proliferating fibroblastic tissue and bizarre masses and trabeculae of osteoid tissue and bone (hematoxylin & eosin, $\times 100$)

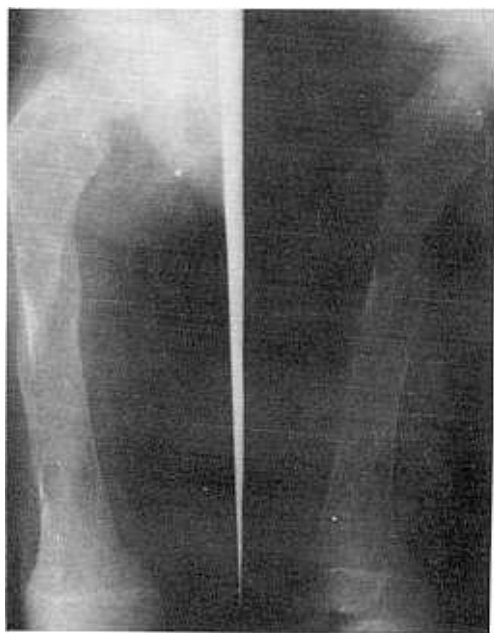


Fig. 4. Plain radiographs demonstrate the healing of fracture of right femur.

but TSH was suppressed.

Glucose tolerance test produced a normal blood-sugar curve. Urine analyses showed neither glycosuria nor proteinuria. Other biochemical investigations and liver function tests were normal. A biopsy in the lucent area of right proximal femur revealed the histologic appearance of fibrous dysplasia (Fig. 3). She was started on 50,000 units of calciferol daily and oral phosphorus. Hyperthyroidism and hypertension were controlled with propranolol. Her fracture was managed conservatively and healed after 7.1 weeks (Fig. 4). In November 1989 she was seen again at Severance Hospital due to another fracture of the right tibia (Fig. 5). She was again treated conservatively. Biochemical investigations performed at that time showed no significant changes. Her general symptoms improved gradually thereafter. The fracture of the tibia healed (Fig. 6) and serum level of phosphorus improved to near normal level at the last follow-up in May 1990.



Fig. 5. Plain radiographs showing repeated fracture of mid-portion of right tibia. Note generalized demineralization and multiple lucent areas with sclerotic margins.



Fig. 6. Plain radiographs showing the healing of fracture of right tibia.

DISCUSSION

Hypophosphatemic rickets secondary to non-endocrine tumors have been reported previously (Ryan and Reiss 1984; Salassa *et al.* 1970). Hemangioma or hemangiopericytoma was the most frequently associated tumor in the literature (Cotton and puffelen 1986), and the tumors, mostly benign, included epidermal blue-nevus syndrome (Aschinger *et al.* 1977), neurofibromatosis (Retnam *et al.* 1980) and fibrous dysplasia (Dent and Gertner 1976). These tumors usually showed the histologic appearance of a fibrous mesenchymal component, and Olefsky *et al.* (1972) and Ryan and Reiss (1984) stressed the mesenchymal derivation of these tumors. The mechanism of induction of hypophosphatemic rickets by neoplastic tissue of mesenchymal origin is not yet completely known. The proposed pathogenesis is that tumor-induced hormone substance(s) may block the conversion of 25 hydroxycholecalciferol to 1.25 dihydroxycholecalciferol

with resultant hyperphosphaturia and hypophosphatemia and may cause functional impairment of phosphate reabsorption in the proximal renal tubule (Fukumoto *et al.* 1979).

The association of polyostotic fibrous dysplasia of bone with patch cutaneous pigmentation and sexual precocity is referred to as McCune-Albright syndrome. Recently, additional endocrinologic disorders have been described as part of this syndrome, including hyperthyroidism, acromegaly, hyperparathyroidism, and Cushing syndrome. Hyperthyroidism is frequently encountered as part of McCune-Albright syndrome, and Benedict (1962) reported the incidence was in the range of 5 to 30 per cent. There are a number of unusual features of hyperthyroidism in these patients. Besides a high frequency in male, the onset of hyperthyroidism in most cases reported were between the age of 3 to 12 years (Zangenah *et al.* 1966), although there have been a few instances of onset in adolescence or adulthood (Moldawer and Rabin, 1966). Coexistence of Cushing syndrome and Albright's syndrome is rare (Benjamin & McRobert, 1973). The interrelationships of thyroid hyperfunction, adrenal hyperplasia or the other endocrinologic disorders with Albright's syndrome is unclear. Hall and Warrick (1972)'s suggestion that the central hypothalamic hyperthyroidism which occurs in association with Albright's syndrome may be caused by hypersecretion of hypothalamic-releasing hormones has failed to materialize. However, detailed review of autopsy findings in Albright syndrome has shown that symptom complexes may, in fact, represent an entity in which multiple organs initially or subsequently function in an autonomous fashion (Danon and Crawford, 1974). The origin of sexual precocity in McCune-Albright syndrome is still in question also. Clinical and laboratory investigations demonstrated that the gonadal function also appears to be autonomous. Thus the premature sexual development in McCune-Albright syndrome is likely a type of pseudoprecocious puberty. D'Armiento *et al.* (1983) observed the low progesterone values, and this study further supports this hypothesis. Together with the data reported by others (Lightner *et al.* 1975; Danon *et al.* 1975) showing cases of McCune-Albright syndrome with autonomous functioning of pituitary, adrenal and thyroid gland, he came to the conclusion that McCune-Albright syndrome must be considered a multiendocrine adenomatosis, as predicted by Digeorge (1975) who put forward peripheral lesion of embryonal origin as possible mechanism. The mechanism of

hypophosphatemic osteomalacia in fibrous dysplasia may not be identical to that associated with mesenchymal tumor (Lever and Pettingale 1983).

Our patient showed hyperthyroidism in addition to hypophosphatemic rickets. There was no evidence of hypothalamo-pituitary dysfunction in view of LHRH stimulation test. Her sexual precocity was regarded as gonadotropin-independent precocious pseudopuberty.

Hypophosphatemic rickets owing to neoplasia has the unique feature of resolution after complete removal of the tumor (Linovitz et al. 1976; Stanbury 1972) Ryan and Reiss (1984) stated that surgical resection of the tumor has resulted in reversal of rickets within 3 to 6 months in 93 per cent of patients. Recognition of this type of rickets is then important because patients debilitated from the symptoms of rickets can return to their normal life. However, many oncogenous rickets may often go undiagnosed in the tumors that were small or difficult to locate. Moreover, tumors which occur in multiple locations are difficult to remove surgically; therefore, complete resolution of hypophosphatemic rickets, as in the case of solitary lesions is difficult to achieve. It is concluded that multiple occurring tumors be treated conservatively with 1,25-dihydroxycholecalciferol combined with oral phosphate supplements. In our patient, rickets was severe enough to cause pathologic fractures repeatedly, but removal of the tumor was not surgically feasible due to its multiple location.

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