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Author(s)	KASAHARA, Katsuyuki; IKEDA, Toshihiko; OKUMURA, Hideo; YAMAMURO, Takao; FUJITA, Atsushi
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EFFICACY OF HOMOGENOUS BONE GRAFTING IN MCCUNE-ALBRIGHT SYNDROME

Katsuyuki KASAHARA, Toshihiko IKEDA*, Hideo OKUMURA*
Takao YAMAMURO*, and Atsushi FUJITA**

ABSTRACT: A case of McCune-Albright syndrome is reported. The patient was a girl aged 8 years. The chief complaints were gait disturbance and a limp. Roentgenograms showed collapse and severe varus deformity of the femoral neck on the right side with 64° of neck-shaft angle. She had an episode of vaginal bleeding at the age 7 years. Valgus osteotomy of the right proximal femur for the correction of coxa vara and a bone transplantation of an allograft from her mother were performed. Seventy degrees of correction were obtained and the discrepancy of limb length was 1cm after the operation. Roentgenograms showed sufficient callus and solid union between the fragments and the grafted bone 1 year after the operation. Frozen allograft bone was very effective in stimulating bone induction even in fibrous lesions of a patient with McCune-Albright syndrome. Immunology of bone grafts, HLA antigens, osteogenesis in grafts, and the etiology of McCune-Albright syndrome were discused.

Key words: McCune-Albright syndrome, Allograft, Bone grafting, HLA.

INTRODUCTION

McCune[1] and Albright[2] have reported a syndrome characterized by the triad consisting of polyostotic fibrous dysplasia of bones (osteitis fibrosa disseminata), endocrine dysfunction with precocious puberty and multiple pigmentation of the skin. The entity of fibrous dysplasia has been accepted by Lichtenstein and Jaffe[3]. They recognized that fibrous dysplasia may be monostotic. The dysplasia of bone starts in early childhood and develops extensively in the patients with McCune-Albright syndrome. Deformities are severer, progression is more marked, and fractures are commoner than in monostotic fibrous dysplasia. Sometimes, functional disorders caused by residual deformities in this disease are very difficult to manage[4]. We will report on the case of a girl with this disease who was treated with valgus osteotomy for correction of coxa vara and with bone transplantation of an allograft from her mother. The usefulness of allografted

Division of General Education, College of Medical Technology, Kyoto University.
* Department of Orthopaedic Surgery, Faculty of Medicine, Kyoto University.
** Department of Orthopaedic Surgery, Ohtsu Red Cross Hospital.
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bone and the immunology of grafted bone will be discussed.

CLINICAL MATERIAL

A girl aged 8 years was admitted to the Kyoto University Hospital on April 11, 1984, because of a severe limp.

She was the first born child and there was no family history of orthopaedic diseases. The mother was healthy and 24 years old at the time of delivery. She did not take any medications during pregnancy. The patient was born on October 5, 1975, three weeks before the expected data of confinement on October 26, 1975, and the delivery was by the breech, the birth weight being 2530 grams. Her growth and psychommotor development were normal. She began to walk independently at fourteen months of age, and she developed a limp at eighteen months of age. The mother stated that the shortening of the right lower limb seemed to increase after the patient sustained contusion in the right thigh at 2 years of age. At the age 4 years, radiological investigations revealed an intertrochanteric pathologic fracture and a large expanding radiolucent area in the right femoral neck (Fig. 1). There was a shortening of 2 centimeters in the femur. The lesion was curetted and packed with autologous bone taken from the right iliac bone in the Ohtsu Red Cross Hospital (Fig. 2). The histological examination showed fibrous dysplasia, which was composed of a mature connective tissue with thin trabecular bone.

Subsequent roentgenograms showed the recurrence of the disease (Fig. 3-A) and the collapse of the femoral neck (Fig. 3-B). At the age 7 years, she had an episode of vaginal bleeding. Endocrinological investigations were carried out by Dr. Takatsuka of

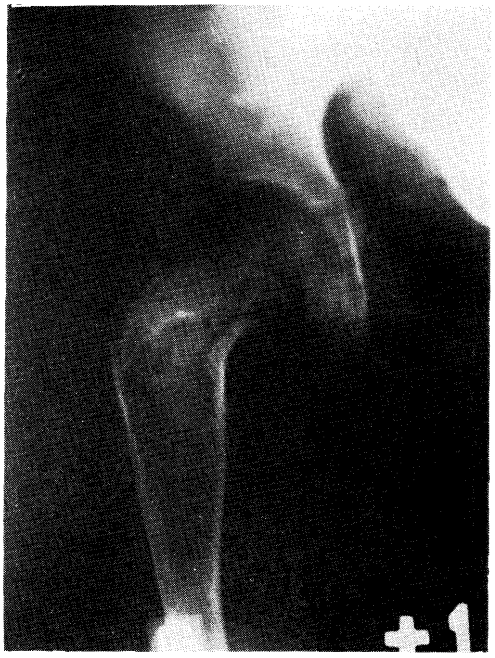


Fig. 1. Roentgenogram shows a large expanding radiolucent lesion in the right femur (15, 5, 1980).

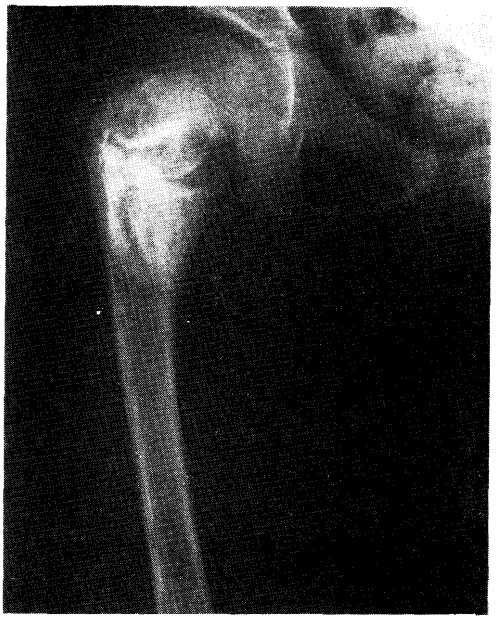


Fig. 2. Three months later after curettage and autologous bone graft (25, 2, 1981).

Shiga Medical School. Menses were stopped after the administration of luteinizing hormone.

The femoral neck became more varus and the right femoral head was atrophic at the time of admission. The subtrochanteric lesion had became enlarged and the femoral shaft had became curved (Fig. 4). Skeletal surveys revealed diffuse rarefaction lesions

Fig. 3-A. Recurrence of the rarefaction lesion in the right femoral neck (25, 3, 1982).

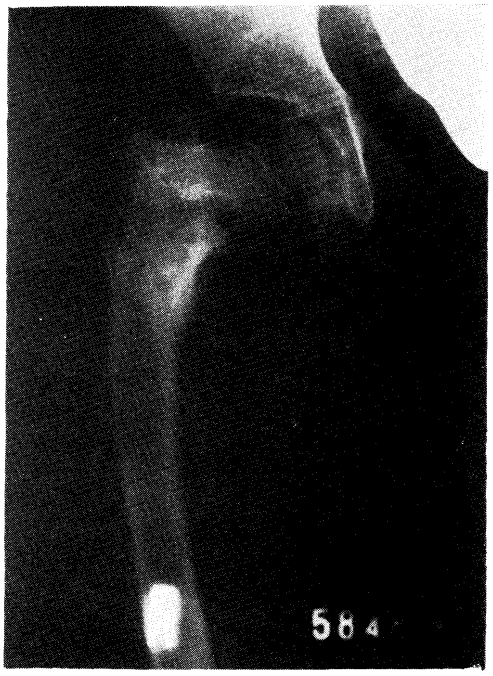


Fig. 3-B. Collapse of the femoral neck (8, 4, 1983).

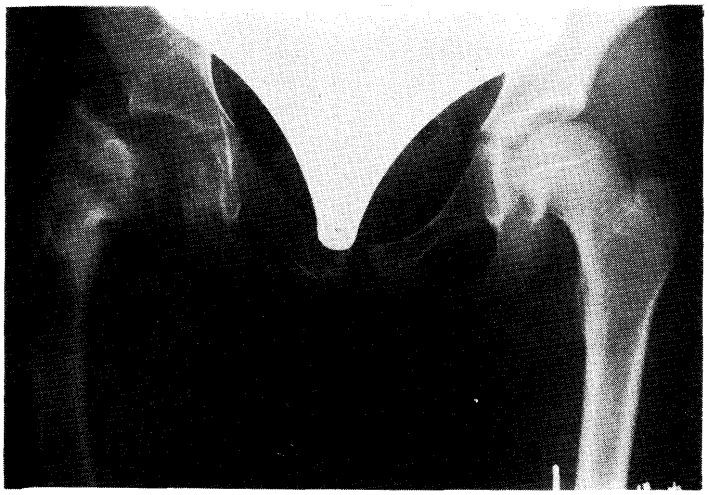


Fig. 4. Severe varas deformity of the right femoral neck and and radiolucent lesions in the right femoral shaft (18, 4, 1984).

Fig. 5. Arthrogram.

in the right humerus, the right femur, and the right tibia. A dense hyperostotic formation had developed in the right side of the facial bones and the skull. Arthrogram showed an inferior pooling of contrast medium and interruption of the recessus (Fig. 5). Computerized tomography scan clearly demonstrated the fibrous change in the femoral neck (Fig. 6-A, 6-B) and sclerotic change in the right side of facial bone (6-C).

The patient's chief complaints were gait disturbance and a limp. There was also some intermittent, dull pain in the affected area.

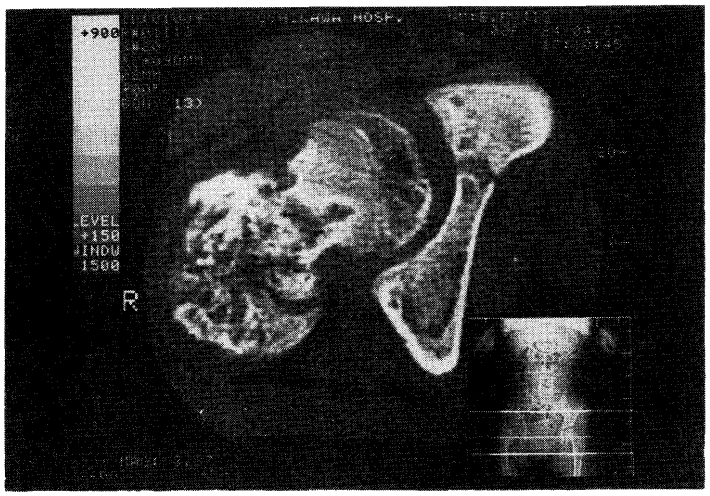
Physical examination revealed 4.5 centimeters true shortening of the right femur, and muscle atrophy in the right thigh and the right leg (Table 1). Flexion and abduction of the right hip joint were limited. Abduction against gravity was impossible, and Trendelenberg's, Duchénne's, and Allis' signs were positive on the right side (Table 1). Café-au-lait spots were not noticed.

Roentogenograms showed 64° of neck-shaft angle on the right side and 142° on the left side. The antiversion angle was 20° on the right side and 22° on the left side.

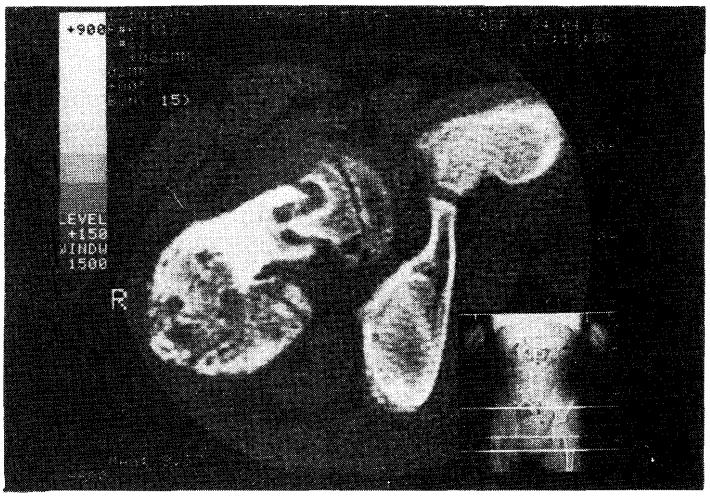
Routine blood analysis is shown in Table

Table 1 Physical examination.

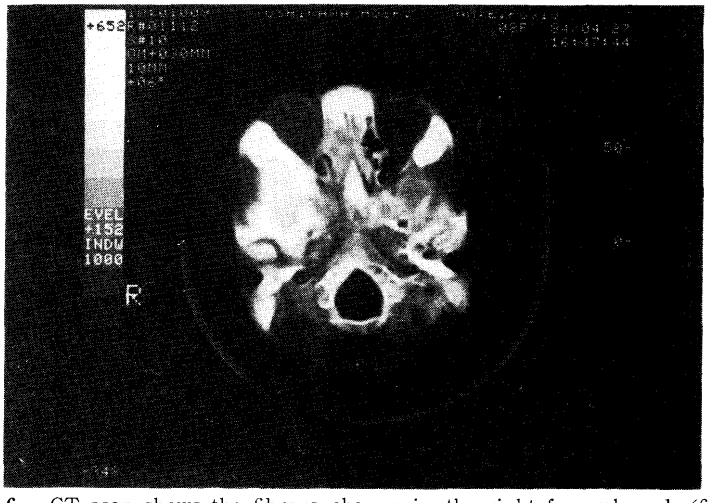
	Right		Left	
	Pre-Ope	Post-Ope	Pre-Ope	Post-Ope
SMD	58.0cm	61.0cm	62.5cm	63.3cm
COT	30.6cm	30.0cm	33.0cm	35.0cm
COL	23.3cm	23.0cm	25.5cm	25.5cm
Hip joint Flexion	120°	120°	135°	135°
Extension	20°	20°	20°	20°
Abduction	18°	35°	35°	35°
Adduction	50°	15°	25°	25°
ER	40°	40°	45°	45°
IR	50°	45°	50°	50°
SLR	100°	100°	100°	100°
AAG	0°	30°	35°	35°
Trendelenberg	++	+	−	−
Allis	++	+	−	−
Duchénne	++	+	−	−



6—A



6—B



6—C

Fig. 6. CT scan shows the fibrous change in the right femoral neck (6-A, 6-B) and sclerotic change in the right facial bone (6-C).

2. The results of serum chemistry were normal except for alkaline phosphatase, the value of which was extensively high. The serum calcium concentration was 9.0mg/dl, and phosphorus 3.7mg/dl. The plasma level of PTH (parathyroid hormone) was within the normal range and calcitonin was not elevated. Hyperthyroidism, acromegaly,

Table 2 Laboratory data.

WBC	4.1×10^9/L	GOT	22 (12—32) IU/L
RBC	4.93×10^{12}/L	GPT	10 (5—26) IU/L
HGB	12.8g/dl	LDH	399 (228—475) IU/L
HCT	38.9%	ALP	487 (15—70) IU/L
PLT	239×10^9/L	TP	6.1 (6.8—8.5) g/dl
PTT	11.1sec	ALB	4.0 (4.0—5.1) g/dl
HB Ag	(−)	T-BIL	0.4 (0.1—0.9) mg/dl
HB Ab	(−)	T-CHO	149 (120—260) mg/dl
CRP	(−)	UA	4.8 (2.4—5.8) mg/dl
ASO	×20	BUN	15 (8—22) mg/dl
VDRL	(−)	GLU	75 (70—110) mg/dl
TPHA	(−)	Mg	2.1 (2.2—3.1) mg/dl
PTH	0.28 (0.5以下) ng/ml	Ca	9.0 (8.2—9.8) mg/dl
Calcitonin	0.064 (0.3以下) ng/ml	P	3.7 (2.9—4.7) mg/dl
		Na	140 (136—146) mg/dl
		K	3.9 (3.6—4.9) mg/dl
		Cl	109 (100—110) mg/dl

Table 3

Type of red blood cell	ABO	Rh
F. E. (Patient)	B	+
F. M. (Father)	AB	+
F. Y. (Mother)	O	+

HLA type	F. E. (Patient)	F. Y. (Mother)	F. M. (Father)
A locus	26, 2	2, W24	26, W31
B locus	W62, W46	W46, —	W62, W52
C locus	X46, —	X46, —	—, —
DR locus	W8, W9	W8, —	2, W9
Others	MT1, MT2, MT3	MT1, MT2	MT1, MT3

Probable HLA halotype

	A	B	C	DR
Patient	26	—	—	—
	2	W46	X46	W8
Mother	W24	—	—	—
	2	W46	X46	W8
Father	26	W62	—	W9
	W31	W52	—	2

hyperparathyroidism, and Cushing syndrome were not noticed. A summary of blood typing and HLA (human lymphocyte antigen) studies is shown in Table 3. HLA typing was performed with a microcytotoxicity test using Japan HLA workshop standard antisera in the Kyoto Red Cross Blood Center.

OPERATION

Valgus osteotomy of the right proximal femur for the correction of coxa vara and a bone transplantation of an allograft were performed on May 4, 1979. The patient was on the left side position under general anesthesia. The posterolateral incision was made from the greater trochanter distally to the lateral femoral condyle. Subcutaneous fatty tissue and fascia lata were incised in the line of skin incision. The dissection was continued down to the bone along the linea aspera. The surface of the femur was exposed by incising and elevating the periosteum. Guide pins were inserted and control roentgenograms were taken. Osteotomy using a power saw was completed as determined in the preoperative drawings (Fig. 7). The iliopsoas tendon was released from the lesser trochanter. Seventy degrees of correction were obtained after reducing and fixing the osteotomy by using a curved plate and screws. The fibrous lesion was not curetted extensively, but some of it was removed for histological examination. Pathological diagnosis was fibrous dysplasia.

A full-thickness liliac graft was taken from patient's mother. The graft was submerged in liquid nitrogen, with a temperature of −196, 6°C., which was transported in a double steel-lined thermos bottle. Two minutes later, the graft was transfered into saline at room temperature for thawing. The graft was frozen three times before transplan-

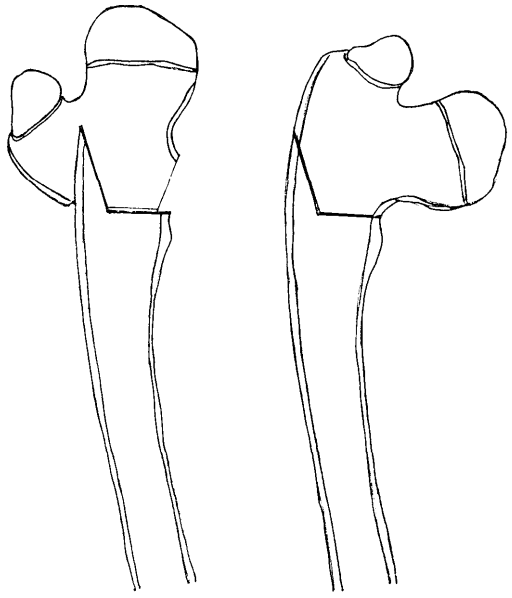


Fig. 7. Valgus osteotomy for correction of coxa vara.

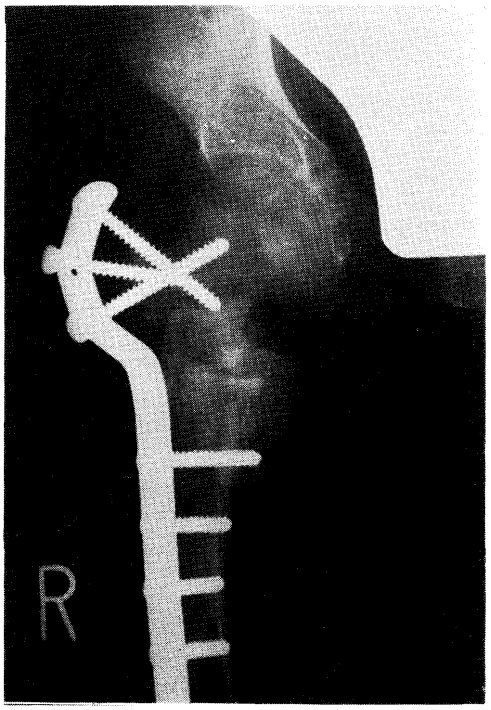
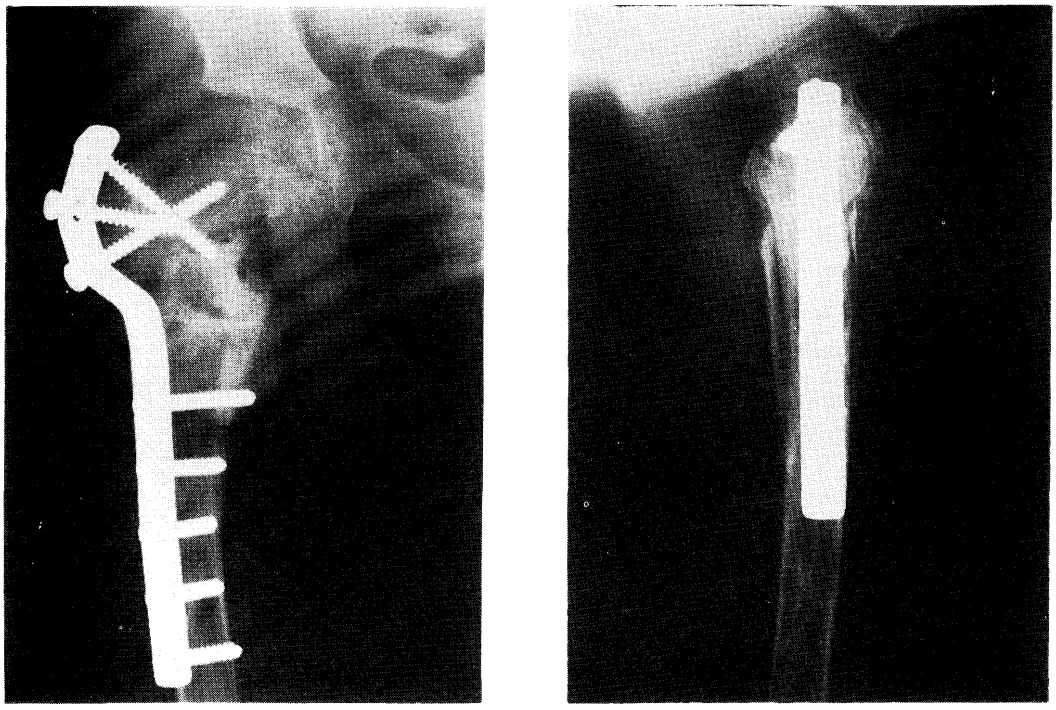


Fig. 8. One month later after the valgus osteotomy (4, 6, 1984).



A B

Fig. 9-A, 9-B. Radiograph demonstrate solid union between the fragments and allografts of bone (23, 9, 1984).

tation after Marcove technique of cryosurgery[5].

A full-thickness bone, the allograft, was transplanted to bridge the bony defect between the proximal and the distal fragment and fixed by one of the screws through the plate. Other allografts were put on the anterior and the posterior surface of the femoral shaft (Fig. 8).

A plaster-of-Paris spica was worn for two months, then a trilateral socket hip orthosis (Tachdjan type)[6] was applied.

Roentgenograms showed sufficient callus and solid union between the fragments and the grafted bone. The discrepancy of limb length was 1cm. (Fig. 9-A, 9-B).

DISCUSSION

DIAGNOSIS AND TREATMENT: The clinical and laboratory studies in this patient revealed polyostotic fibrous dysplasia of bone combined with precocious puberty. This case is virtually consistent with McCune-Albright syndrome except skin pigmentation was not noticed. Osteitis fibrosa generalisata (hyperparathyroidism), Ollier's disease (dyschondroplasia), Paget's disease (osteitis deformans), osteogenesis imperfacta (Periosteal dysplasia), and neurofibromatosis were all inconsistent. A number of hormone excess endocrinopathies[7,8], which have been recently described as part of the syndrome, was not noticed except for sexual disorders.

Harris et al[4]. are of the opinion that curettage and bone grafts, which are effective in adult patients with monostotic fibrous dysplasia, could not cure polystotic fibrous

dysplasia in childhood, and that treatment should be conservative as the lesions commonly stop growing at puberty. According to their report, lesions progressed in six patients before puberty and eight patients after puberty. However, repeated fractures and bowing of the large lesions in the weight-bearing bones often resulted in severe residual deformity and marbek functional disturbance, for instance, Shepherd's crook deformity in the femoral neck. They consider surgical treatment advisable only in the presence of significant or progressive deformity, non-union of fracture, and persistent pain unresponsive to conservative treatment. In our case, the functional distubance in the right hip joint because of severe varus deformity and limb shortening required an operation, valgus osteotomy and bone grafts. As the patient's iliac bone was too thin and small, her mother's bone was used instead.

BONE GRAFTING: The use of bone grafts is a well established procedure in the field of orthopaedic surgery since 70 years ago[9]. Usually, autogenous bone (patient's own bone, autograft) has been used for grafting in many conditions. Heterogenous bone (bone of different species, xenograft) or homogenous bone (another human's bone, allograft) can be used nowadays after chemical or biological treatment. Another human's bone or the bone of a cross-species used as a graft material may provoke immunological responses in the host.

IMMUNOLOGY OF BONE GRAFTS: Bone tissue consists of red marrow cells (haematopoietic cells), osteoprogenitor cells and collagenous calcified matrix with proteoglycans. Humoral immune and cellular immune responses of the host are mainly elicited by the cellular components of the graft[10,11,12]. An allograft with the red marrow resulted in a greater immune response than the bone tissue itself[10,11]. Medawar proved that skin homograft rejection depends on the compatibility of donor antigens for recipient[13]. The most important antigens concerning the transplantation immunity in human beings is human lymphocyte antigen (HLA).

HLA: Human lymphocyte antigen, which is determined by the genetical loci in the major histocompatibibility complex (MHC), consists of MHC class 1 antigens (HLA-A, HLA-B, HLA-C) and MHC class 2 antigens (HLA-DR, HLA-BR). All kinds of cells in the human body except red blood cells possess MHC class 1 antigens. Cells which constitute bone tissue (osteocytes, periosteal cells, endosteal cells, marrow cells) also possess class 1 antigens. MHC class 2 antigens, namely HLA-DR ($\alpha_1\beta_1$) antigen and HLA-BR ($\alpha_1\beta_2$) antigen, are detected in B-lymphocytes and monocytes.

It has been reported that bone grafts with marrow cells elicit a much stronger response than bone tissue itself for the following reasons.

(1) Class 2 antigens are the most significant ones concerning graft rejection[14]. They are possessed by the limited cells, i.e., B-lymphocytes and monocytes, and are not detected in osteoprogenitor cells. Class 2 antigens are thought to stimulate MLR (allogenic mixed lymphocyte reaction).

(2) Osteocytes possess antigens of the class 1 major histocompatible-antigen system. They are antigenic but only feebly immunogenic. The bone canaliculi may be too small to allow the host immune cells to gain access to them and the matrix proteoglycans protect the cells, a mechanism which has been postulated

by White[15].

(3) Friedenstein et al[16]. have reported that haematopoiesis in the grafted cancerous bone continued for a few weeks, and that GVH (graft versus host) reaction may happen in situ.

OSTEOGENESIS IN GRAFTS: Many researchers[12,17,18] have been supporting the two-phase theory of osteogenesis proposed by Axhausen[19]. The two phases are these: First, osteogenesis is carried out by the cells of the grafted bone mainly during the first few weeks (first phase), and second, cells derived from the recipient start to contribute significantly to new bone formation 4 or 5 weeks after a fresh bone autograft or isograft (second phase).

Burwell has investigated the osteogenic induction of allografts and shown that allogenic bone stimulated osteogenesis to a similar extent as did autografts[20].

Urist et al. found decalcified, freezedried allogenic bone to be a potent inductive stimulus for new bone formation in rats[21].

In our case, there were four miss matches of HLA antigens between the donor and the recipient. The bone graft was frozen three times and rinsed to remove the cells in the bone marrow. Subsequent roentgen ograms followed up after the operation revealed solid bone union between the grafted bone and recipient's femur. Frozen allograft bone was very effective in stimulating bone induction even in fibrous lesions of a patient with McCune-Albright syndrome.

HYPOTHESIS ABOUT THE ETIOLOGY OF McCUNE-ALBRIGHT SYNDROME. Hall and Warrick have proposed a single hypothalamic origin of the disease[22]. They have suggested that endocrine associations may be the result of a congenital hypothalamic abnormality causing overproduction of a variety of releasing hormones which are responsible for the pituitary overactivity and increased function of the target organs. Sexual precocity, hyperthyroidism, acromegaly, accelerated skeletal growth and maturation, Cushing's disease, and gynaecomastia were all explained as being caused by a central mechanism. On the other hand, DiGeorge[23] and Giovannelli et al[24]. consider the McCune-Albright syndrome similar to multiple endocrine adenomatosis, which is explained as a congenital dysplasia of some of the common stem cells which differentiate into ectodermal and endodermal endocrine glands[25].

Polystotic fibrous dysplasia of bone is indicated by scattered lesions which have a marked tendency to be unilateral. This unilaterality does not suggest the involvement of bone caused by the central mechanism of hypersecretion of hypothalamic hormones. The dysplasia of bone seems to result from scattered clones which have a congenitally abnormal reactivity of osteogenesis. Bony lesions (mesodermal derivative) may be one type of pleiotropic, scattered peripheral lesion of embryonal origin.

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