Polyostotic Fibrous Dysplasia in a Young Female with McCune Albright Syndrome

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Abstract

Background and Significance: McCune Albright Syndrome (MAS) is a rare disorder characterized by the clinical triad of precocious puberty, polyostotic fibrous dysplasia of the bones and café-au-lait spots. Prevalence is estimated at 1/100,000-1/1,000,000. We report a case of polyostotic fibrous dysplasia in a patient with McCune Albright Syndrome who had symptomatic relief of hip pains and non-recurrence of stress fractures in a dysplastic right hip bone following treatment with loading intravenous pamidronate followed by an oral alendronate for almost a year, as an off-label indication. While intravenous bisphosphonates have been well-recognized in the treatment of fibrous dysplasia, only case reports are available to support its utility.

Case Report: We report an 18 year old female with leg length discrepancy following repeated episodes of hip fracture for the past six years. She was referred to the Philippine General Hospital for recurrent severe leg pains which occurred usually at menstrual mid-cycle. This condition was associated with lateral bowing of the proximal part of the right thigh, widening of the right hip region, and shortening of the right lower limb also known as Shepherd’s Crook deformity. She also had café-au-lait spots at the back of her left legs and buttocks. Skeletal survey showed radiolucent medullary expansile lytic lesions with ground glass appearance of the right femur, tibia, fibula, humerus, scapula, pubis, ischium, carpal and metacarpal bones. Patient was noted to have short stature with height of 142 cm. Arm span was 139 cms, upper body segment (crown to the coccyx) was 70cms while lower body segment (coccyx to heel left foot) was 72 cms. The difference between the left and right leg was 7 cms. Mean parental height was 160 cm. She was then referred to the Endocrinology service of this institution for evaluation of the short stature and associated endocrinopathies.

On review, she had adrenarche at 8 years old followed by menarche at 10 years old. She had no goiter. She had no cushingoid features. Patient had irregular menstrual cycles with oligomenorrhea (cycle: 60-180 days). Breast development and pubic hair were staged Tanner 5. In the approach to short stature where height age is less than either the bone age or chronological age, constitutional dwarfism, hypothyroidism, growth hormone deficiency and fibrous dysplasia must be ruled out. Constitutional dwarfism was ruled out with a midparental height of 160 cm. A normal free thyroxine (17, normal: 9.2-39 pmoL/L), thyroid stimulating hormone (2.4, normal: 0.25-4 uIU/ml) ruled out hypothyroidism, and a normal IGF-1 (103, normal: 91-223 nmol/L) ruled out growth hormone deficiency. This left us with the consideration of fibrous dysplasia of the bone which was consistent with the earlier radiographic findings. The combination of polyostotic fibrous dysplasia and café au lait spots led to the impression of McCune Albright Syndrome. The most common endocrinopathy associated with McCune Albright Syndrome is a peripheral hyperfunctioning ovaries which also harbors the G-protein mutation. This was evident in our case with a high estrogen (655.8, normal: 50-250 pg/ml) and suppressed LH (1.2, normal: 1.5-5 pg/ml) and FSH (3, normal 3.5-12.5 pg/ml) with a transrectal ultrasound finding of a 2.6 x 1.7 x 1.6 cm cyst at the right ovary. This precipitated the precocious puberty and early closure of the epiphyseal plates resulting to short stature. To screen for other endocrinopathies, a 24 hour urine free cortisol (44, 20-90 ug/day), serum prolactin (15ng/ml, normal: 0-30ng/ml), free thyroxine (17, normal: 9.2-33.2 pmoL/L) and parathyroid hormone (13.9, normal 10-65pg/ml) was documented and ruled out associated hypercortisolemia, prolactinoma, hyperthyroidism and hyperparathyroidism respectively. The patient had no history of change in shoe size, and no coarsening of facial features that was suggestive of acromegaly.

Treatment: Patient underwent bone grafting and osteotomy to correct the shepherd’s crook deformity. Three cycles of intravenous pamidronate infusion in three consecutive days was given prior to the operation. Post-operatively, patient tolerated the procedure and was discharged after three days.

Outcome: Shepherd’s crook deformity was successfully corrected. Patient still had limp but with no pain and no new fractures for almost a year already. At present she is maintained on alendronate 70mg 1 tab once a week and calcium 1 gram per day.

Conclusion: We report a case of McCune Albright Syndrome in a young female with polyostotic fibrous dysplasia and café-au-lait spots who had symptomatic relief of hip pains and non-recurrence of stress fractures following treatment with loading intravenous pamidronate followed by an oral alendronate for almost a year, as an off-label indication.
Syndrome presenting with bone deformity which was later diagnosed to be fibrous dysplasia with polyostotic involvement, and was successfully treated with initial intravenous bisphosphonates maintained on oral bisphosphonates following a surgical procedure to correct the shepherd’s crook deformity. At present, she has had no new fractures.

**Keywords:** McCune Albright Syndrome, cafe-au-lait spots, fibrous dysplasia

**Introduction**

McCune-Albright Syndrome (MAS) is a rare disorder characterized by the classic triad of precocious puberty, polyostotic fibrous dysplasia and cafe-au-lait spots. Estimated prevalence is 1/100,000-1/1,000,000. In addition, a myriad of potential endocrinopathies can also be seen. The extent of the manifestations is highly variable, depending on the specific tissues involved due to the mosaic distribution of the GNAS1 mutation. Presented is a typical case of McCune Albright Syndrome with characteristic fibrous bone dysplasia, successfully treated with intravenous and oral bisphosphonates.

**Case Report**

This is a case of an 18 year old female, from Cavite, who presented with severe bone pain and bone deformity. Patient was apparently well until six years prior to consultation, patient accidentally slipped off the ground and fell on her right hip while walking. No medical consultation was done. Since then, patient was noted to be limping, with obvious leg length discrepancy. However, condition was just tolerated until a year later when she experienced leg pain with increasing intensity prompting her to seek medical consultation. Radiological examination of the right hip and femur showed an expansile radiolucent filling defect in the right femur was made. In a patient with fibrous dysplasia, there are three other conditions must be ruled out. A simple radiography can differentiate these conditions. First is a simple bone cyst, usually monostotic and more radiolucent. Second is an osteosarcoma which has denser mineralization compared to fibrous dysplasia and is more aggressive overtime. Our patient had less dense skeletal lesion and her condition evolved over six years. Third is Paget’s disease which is mostly monostotic involving flat bones although a polyostotic long bone involvement may also occur. Usually males are affected in their mid 20s to 30s and are of Northern European ancestry. Our patient was only 18, female and without a European descent. But the most distinguishing feature of Paget’s disease is a markedly elevated alkaline phosphatase. Our patient had only slightly elevated alkaline phosphatase (104, normal value 25-90U/L). Skeletal survey showed radiolucent medullary expansile lytic lesions (refer to pictures below), with ground glass appearance of the right femur, fibia, fibula, humerus, scapula, pubis, ischium, carpal and metacarpal bones. Shepherd’s crook deformity (lateral bowing of the right proximal femur) was also seen. Multiple lucencies were also noted in the skull with endosteal scalloping and sclerosis of the right skull base. The sella was normal in configuration. The features were consistent with polyostotic form of fibrous dysplasia. Fibrous dysplasia occurs a result of a developmental failure in the remodelling of primitive bone to mature lamellar bone and a failure of the bone to realign in response to mechanical stress. Failure of maturation leaves a mass of immature isolated trabeculae enmeshed in dysplastic fibrous tissue that are turning over constantly but never completing the remodelling process. An immature matrix does not mineralize normally despite normal calcium intake and vitamin D levels which differentiate them from osteosarcoma radiographically. Serum ionized calcium (1.16, normal 1-1.3mmol/L), phosphorus (3.5, normal 2.5-4.6mg/dl) and vitamin-D (55, normal 40-100nmol/L) were all normal. The lack of stress alignment and insufficient mineralization resulted in substantial loss of mechanical strength leading to development of pathologic fractures, deformity and pain. Shepherd’s crook deformity is a classic deformity of polyostotic fibrous dysplasia which is reflected clinically as lateral bowing of the proximal thigh, widening of the hips and shortening of the limb as seen in our patient. This deformity is a result of intermittent stress fractures through the dysplastic bone which deforms from normal mechanical forces. Since dysplastic bones are poorly mineralized, primary hyperparathyroidism and vitamin D deficiency must also be ruled out as a cause of decreased bone mineralization. Parathyroid hormone and 25-cholecalciferol levels were normal (13.9, normal: 10-65 pg/ml) and (55, normal: 40-100nmol/L), respectively.

On further physical examination, hyperpigmented patches with irregular borders were observed at the back of the left leg and buttocks. These were cafe au lait spots in comparison to irregular borders were observed at the back of the left leg and buttocks. These were cafe au lait spots in comparison to smooth bordered lesions seen in neurofibromatosis. These large, light brown areas, with irregular, jagged borders may appear anywhere on the skin, and they characteristically start or stop at midline of the stomach in front, or at the spine in the back. In some, it may not be noticeable, or may be confined to a very small area in the back of the neck or the crease of the buttocks, thus the importance of thorough physical examination.

The presence of polyostotic fibrous dysplasia and cafe-au-lait spots lead to the impression of MAS. Patient was then referred to our service for work-up for associated endocrinopathies.
Her mother had non-toxic goiter. No similar condition as that of the patient was noted in her family members. She had adrenarche at 8 year old, followed by menarche at 10 years old. Menstrual cycles however were irregular (cycle: 60-180 days). Patient weighed 39 kg. With height of 142 cm (body mass index: 19.3 kg/m2). Arm span was 139 cms; upper body segment (crown to the coccyx) was 70 cms while lower body segment (coccyx to heel left foot) was 72 cms. Difference between the left and right leg was 7 cms. Mean parental height was 160 cm. No cushingoid appearance noted. Breast development and pubic hair growth were staged Tanner 5.

In a patient with short stature, bone age, chronological age and height age have to be determined. Bone age is the age for which the bone maturation occurred evidenced with the fusion of the epiphyseal cartilage plate and was consistent of adult age (at least 18 years) fro our patient. Chronological age is the patient’s calendar age and height age is the age for which height is average. In our patient, height age (approximates only that of 13 year old female child) was less than either the chronological or bone age. Considerations for this type are familiar normal variant, chromosomal anomalies, and bone dysplasias. Familial short variant was excluded with the mid-parental height of 160 cm. To work-up for secondary causes of short stature growth hormone deficiency, hypothyroidism, and hypoparathyroidism must also be ruled out. Nutritional deficiency was less likely because of a normal body mass index. She had no history of chronic illness. A normal parathyroid hormone (13.9 normal: 10-65 pg/ml), free thyroxine and thyroid stimulating hormone (FT4: 17, normal: 9-23.2 pmol/L; TSH: 2.4, normal 0.25-4 ulU/ml) and IGF-1 (103, normal: 93-223 nmol/L) ruled out primary hypoparathyroidism, hypothyroidism, and growth hormone deficiency respectively.

Since the most common endocrinopathy seen in MAS is peripheral precocious puberty, estradiol, LH, FSH were taken. Peripheral precocious puberty is caused by an autonomously hyperfunctioning ovary harbouring the GNAS-1 mutation. She had an elevated estradiol (655.8, normal: 50-250 pg/ml) and suppressed LH (1.2, normal 1.5-5 pg/ml) and FSH (3.5 normal 3.5-12.5 pg/ml). Transrectal ultrasound showed presence of a unilocular anechoic cyst in the right ovary, measuring 2.6 x 1.7 x 1.6 cm. This hyperfunctioning ovary led to the premature closure of the epiphyseal plate leading to short stature and hypoplastic bone formation, which explains the cafe-au-lait spots.

**Fig. 1.** Cafe-au-lait Spots at the Back of the Buttocks and Legs. Closer View Revealed Irregularly Bordered Hyperpigmented Areas.

**Fig. 2.** Fibrous Dysplasia at Different Sites. In A: Shepherd's Crook Deformity B: In the Humerus C: Glass Bottle Stopper Illustrating the Hazy Appearance of Ground Glass D: Fibrous in the skull e: Fibrous in the Tibia F: Fibrous in the Metacarpals.
early development of secondary sexual characteristics. In the review of Shozu, peripheral precocious puberty was seen in 89 percent of cases.1 Other endocrinopathies included hypercortisolism (7%) acromegaly (5%), prolactinoma (4%), hyperthyroidism (3%), hyperparathyroidism (1%) and macro-orchidism (1%).1 A normal 24-hour urine free cortisol (44, 20-90 ug/day), serum prolactin (15ng/ml, normal: 0-30ng/ml), free thyroxine (17, normal: 9-23,2 pmol/L) and parathyroid hormone (13.9, normal 10-65pg/ml) were documented and ruled out associated hypercortisolemia, prolactinoma, hyperthyroidism and hyperparathyroidism respectively. The patient had no history of change in shoe size, and no coarsening of facial features that was suggestive of acromegaly.

The occurrence of fibrous dysplasia, cafe au lait spots and peripheral precocious puberty led to the diagnosis of MAS.

The patient underwent bone grafting and osteotomy to correct the shepherd’s crook deformity. Three cycles of intravenous pamidronate infusion in three consecutive days was given prior to the operation. Post-operatively, patient tolerated the procedure. At present, she has been maintained on alendronate 70mg 1 tab once a week and calcium 1 gram per day for almost a year. She still had a limp but with no pain and had no recurrence of fractures.

Discussion

MAS is a rare multisystem disorder, which in its classic form, consists of at least two features of the triad of fibrous dysplasia, cafe-au-lait spots and multiple endocrine dysfunction, most commonly precocious puberty.1 It affects females more often than male by a ratio of about 3:2.1,2 The syndrome occurs equally in all races.2 The estimated prevalence is 1/100,000-1:1,000,000 and was first described in the mid 1937 by McCune and Albright.2,3

MAS may be apparent at birth based upon the presence and recognition of the characteristic skin pigmentation. However, in many cases, the disorder may not be apparent until late infancy or childhood, when precocious puberty develops, or when bone deformities become obvious. In this patient, the diagnosis of MAS came into play when she sought consult for bone deformity associated with severe bone pain.

MAS is the result of a postzygotic somatic mutation in the gene coding for the alpha subunit of the stimulatory G protein.1,4 The specific mutation that causes MAS occurs at a site in the protein that mediates the inactivation of the Gs alpha subunit located at chromosome 20.4,5 Once activated, the mutated GS alpha subunit remains activated for a prolonged period despite the absence of hormone stimulation of the receptor, resulting in constitutive cAMP activation.6 In various tissues, increased cAMP levels can mediate mitogenesis and increased cell function.6 Since it presents in mosaic form, not all body tissues will be affected, and manifestations vary in severity. And since this mutation occurs after fertilization (post-zygotic), it is not inherited from the parents.5 The increase in cAMP triggers the release of IL-6 which is responsible for activation of osteoclast and subsequent bone resorption.6 The increase in cAMP also activates the c-fos proto-oncogenes which activates the fibroblast causing the fibrous dysplasia.6

The range and severity of symptoms and physical characteristics associated with MAS vary greatly among affected individuals, according to the specific body cells and tissue affected. Fibrous dysplasia is a common feature in MAS, and it may range from asymptomatic lesions to markedly disfiguring involvement of the skull, spine and long bones, as observed in this patient. The bony lesions are usually not uniformly distributed, and tend to be unilateral.5 Involvement of the skull is particularly problematic, as lesions near the orbit can result in visual loss and/or proptosis, while lesions near the inner and middle ears can result in deafness and vertigo. Our patient had skull and facial bone involvement radiographically, but she had neither complaint of visual nor auditory changes. Aside from the gross disfigurement, affected individuals may also experience bone pain and frequent bone fractures in affected areas.

Children with MAS usually grow more rapidly than normal, leading to tall stature during childhood, together with the premature onset of secondary sex characteristics.7 However, growth may stop prematurely due to early epiphyseal closure brought about by the increased estradiol levels, so that affected individuals usually does not achieve normal adult height,7 as seen in this patient. In addition, some patients with fibrous dysplasia may manifest with concomitant hypophosphatemic rickets or osteomalacia, resulting from renal phosphate wasting. In this patient, the serum phosphorus level was normal.

The treatment of MAS is mainly symptomatic and supportive. Since the chief complaint of the patient was bone pain and lower limb deformity, the focus of treatment was on the bone lesions. The treatment of choice depends on the age of the patient, severity of symptoms, and the size and location of bone lesion. Orthopedic correction was contemplated due to presence of progressive deformity and unrelenting chronic pain. Patient was subjected to three cycles of intravenous pamidronate (60 mg of intravenous pamidronate for three consecutive days), followed by weekly 70 mg of oral alendronate to improve bone strength and increase cortical thickness, prior to surgical intervention. The use of intravenous pamidronate in fibrous dysplasia has been proposed 15 years ago. A open-labeled study on 58 patients with fibrous dysplasia, treated with intravenous pamidronate every six months, showed significant decrease in pain intensity, and biochemical markers of bone turnover (64% of patients have more than 30% decrement in urinary bone turnover markers).8 Half of the patients also had radiological improvement of bone lesions, evidenced by filling of osteolytic lesions and/or cortical thinning.8 In a study by Lane,8 six patients with fibrous dysplasia were treated with oral alendronate, four patients with fibrous dysplasia
were treated with intravenous pamidronate followed by oral alendronate and two patients were treated with intravenous alendronate alone. After a minimum of two years follow-up, all patients had significant clinical improvement and an average decrease in the pain scores of 74 percent. There was no difference between patients treated with oral bisphosphonates alone and those with intravenous pamidronate followed with oral bisphosphonates. No new fractures developed during the follow-up period. However, in a study by Chan et al, among the three children given intravenous bisphosphonates from age 2.5-5 years old, for 8-10.5 years, dysplastic lesions present in the long bones continued to undergo uncontrolled expansion.10 While intravenous bisphosphonates have been well-recognized in the treatment of fibrous dysplasia very little is known about the efficacy of oral bisphosphonates in fibrous dysplasia. Despite the lack of large scale studies, there are case reports on patients treated with oral alendronate alone who showed improvement in pain, radiographic findings and bone turnover markers. Oral alendronate therefore is a useful, cheaper alternative in the treatment of this condition. In our patient, significant decrease in the severity of bone pain was noted following once cycle of intravenous pamidronate. There has been no new-onset fracture after one year of treatment with oral alendronate.

Prognosis of the patient will depend on the extent and severity of involvement and tissue distribution of the stimulatory G protein mutation. This patient was fortunate in the sense that the disorder was limited to the bones. However, since the fibrous dysplasia has involved the skull and facial bones, there is still a threat on impingement of the optic and auditory nerves with subsequent visual and hearing loss.

**Conclusion**

We report a case of McCune Albright Syndrome presenting with bone deformity which was later diagnosed to be fibrous dysplasia with polyostotic involvement, and was successfully treated with initial intravenous bisphosphonates and maintained on oral bisphosphonates following a surgical procedure to correct the shepherd’s crook deformity. At present, she has no new fractures.

**References**

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