Pharmacogn J. 2024; 16(3): 706-710
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
www.phcogj.com

Case Report

A Girl with McCune-Albright Syndrome: Case Study

Khairunnisa, Muhammad Faizi*, Nur Rochmah,Yuni Hisbiyah, Rayi Kurnia Perwitasari

ABSTRACT

McCune-Albright syndrome (MAS) is a rare genetic disease characterized by skeletal, cutaneous, and endocrine system involvement. We report a 6-year-old girl with fibrous dysplasia, café-au-lait macula, and multiple hyperfunctional endocrinopathies. Treatment was palliative, the patient was planned for surgery on bilateral femur fractures and a rehabilitation program.

Khairunnisa, Muhammad Faizi*, Nur Rochmah,Yuni Hisbiyah, Rayi Kurnia Perwitasari

Department of Child Health, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Academic Hospital, Surabaya, INDONESIA.

Correspondence

Muhammad Faizi

Department of Child Health, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Academic Hospital, Surabaya, INDONESIA.

E-mail: muhammad.faizi@fk.unair.ac.id

History

- Submission Date: 17-05-2024;
- Review completed: 07-06-2024;
- Accepted Date: 10-06-2024.

DOI : 10.5530/pj.2024.16.119

Article Available online

http://www.phcogj.com/v16/i3

INTRODUCTION

McCune-Albright syndrome (MAS) is a rare, non-hereditable genetic disorder characterized by a triad of classic features of fibrous dysplasia, café-au-lait skin macules, and hyperfunctional endocrinopathy.[1] This condition is caused by mutations in GNAS leading to an elevated in intracellular cAMP levels.[2] Clinical findings are commonly used to diagnose McCune-Albright syndrome (MAS). In fact, the management is clinically difficult due to the variety of clinical manifestations that lead to broad differential diagnoses. A multidisciplinary team consisting of multi-specialists is required to monitor patient care. The prognosis may be difficult to determine due to the varying severity of the disease.[3] This report aims to provide information about the patient's symptoms, and how to diagnose and manage patients with MAS. This case was designed to help people become more proficient at comprehending this rare disease.

CASE REPORT

A 6-year-old Javanese girl patient had a history of recurrent fractures at various sites since she was 3 years old. All previous fractures had been successfully managed conservatively. This patient regularly visits an orthopedist and was diagnosed with a primary bone tumor polyostotic fibrous dysplasia.

Her breast budding was at 9 months of age. The history of abnormal genital bleeding began when she was 2 years old and lasted for approximately 6 days, about 3–4 times a year. The parent reported that their child looked taller than her age since she was 2 years old. There was no fever or shortness of breath. There were no complaints of voiding or defecation. Her appetite has increased since last year, but she remains skinny and is getting more irritable. The patient was initially admitted to the pediatric surgery department for two days. The patient was referred to the pediatric endocrinology by the orthopedist department regarding the results of the thyroid hormone test.

Vital signs examination tachycardia 150 x/min, blood pressure 100/60 mmHg x/min, respiratory rate 23 x/min, temperature 36.9 °C, and SpO2 99% in free air. The child's weight, height, and head circumference were at the 75th percentile, 90th percentile, and 98th percentile, respectively, mid parental height at P3-50. There was neither exophthalmos nor thyroid enlargement. The heart, lungs, and abdomen were normal. A café-au-lait macule with jagged borders measuring 5 cm x 3.5 cm on the back along the midline (Fig 2). Breast development was graded as stage II according to Tanner staging. There are deformities in the upper 1/3 of the humerus dextra, and the upper 1/3 of the femur dextra.

Laboratory investigations revealed increased levels of estradiol 118 pg/mL (normal range 10-24 pg/mL), prolactin 58 ng/mL (normal range: 5–20 ng/mL) with LH level 0.04 mUI/mL (normal range 0.02-4.7), and FSH level < 0.030 mUI/ml (normal range 1.0-10.80 mUI/ml). The thyroid evaluation showed suppressed TSH < 0.0083 ng/mL, high level T3 55 ng/mL, and normal fT4 1.24 ng/mL. The adrenal evaluation showed normal cortisol (3.5 µg/dL) concentrations.

Abdominal ultrasonography was performed and showed a uterine size of +/- 3.15 x 3.26 x 4.42 cm (volume +/- 23.7 ml) with an F-C ratio of 2.7: 2, tubular shape, with no visible mass/cyst, and CDUS mapping examination showed normal vascularity. The right adnexa measured +/- 2.21 x 2.26 x 2.20 cm (volume +/- 5.7 ml), with no visible solid/cystic lesions. No solid/cystic lesions were seen in the left adnexa. Based on the examination, the patient's uterine volume was +/- 23.7 ml, which is similar to a 12-year-old girl.

We also conducted a bone age radiograph on the left hand and the findings were consistent with the bone age of a 10-year-old girl (according to S. Idell Pyle).

A dynamic bone scan was performed in 2022. The vascular images showed radiopharmaceutical flow in the distal right humerus increased over time, while the blood-pool images showed the increased uptake of radioactivity in the right humerus and proximal right ulna-radius. Compared to the vascular phase and blood pool, the radioactivity uptake increased. Pathological radioactivity was also observed in the distal 1/3 of the left humerus, proximal 1/3 of the left ulna radius, proximal 1/3 of the left femur, along the right femoral projection, and the medial tibia

Cite this article: Khairunnisa, Faizi M, Rochmah N, Hisbiyah Y, Perwitasari RK. A Girl with McCune-Albright Syndrome: Case Study. Pharmacogn J. 2024;16(3): 706-710.

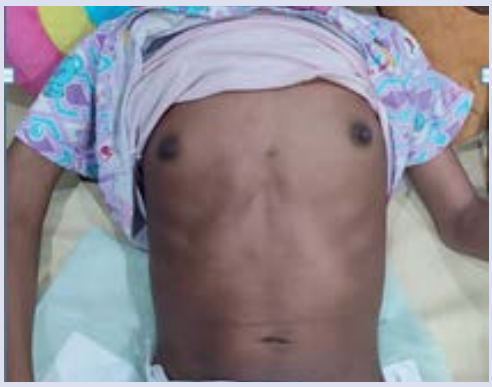


Figure 1. A 6-year-old female patient with nipple hyperpigmentation.

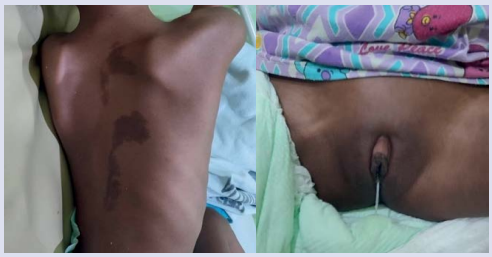
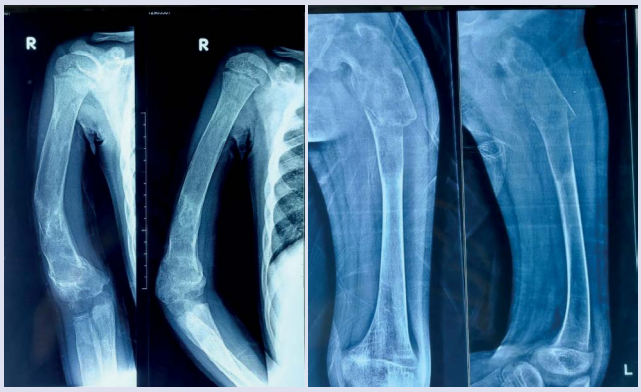


Figure 2. (a). Café-au-lait macule with jagged borders along the midline of the back. (b). Hyperpigmented labia minora.



(a) (b)

Figure 3. **(a)**. Fracture malunion of humerus dextra. **(b).** Closed fractures of the proximal femur sinistra.

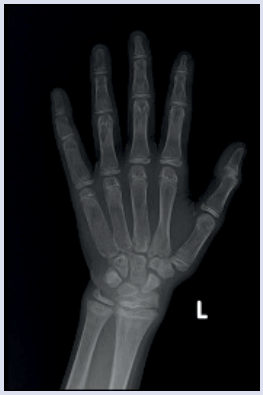


Figure 4. Bone age radiograph findings are consistent with the bone age of a 10-year-old girl.

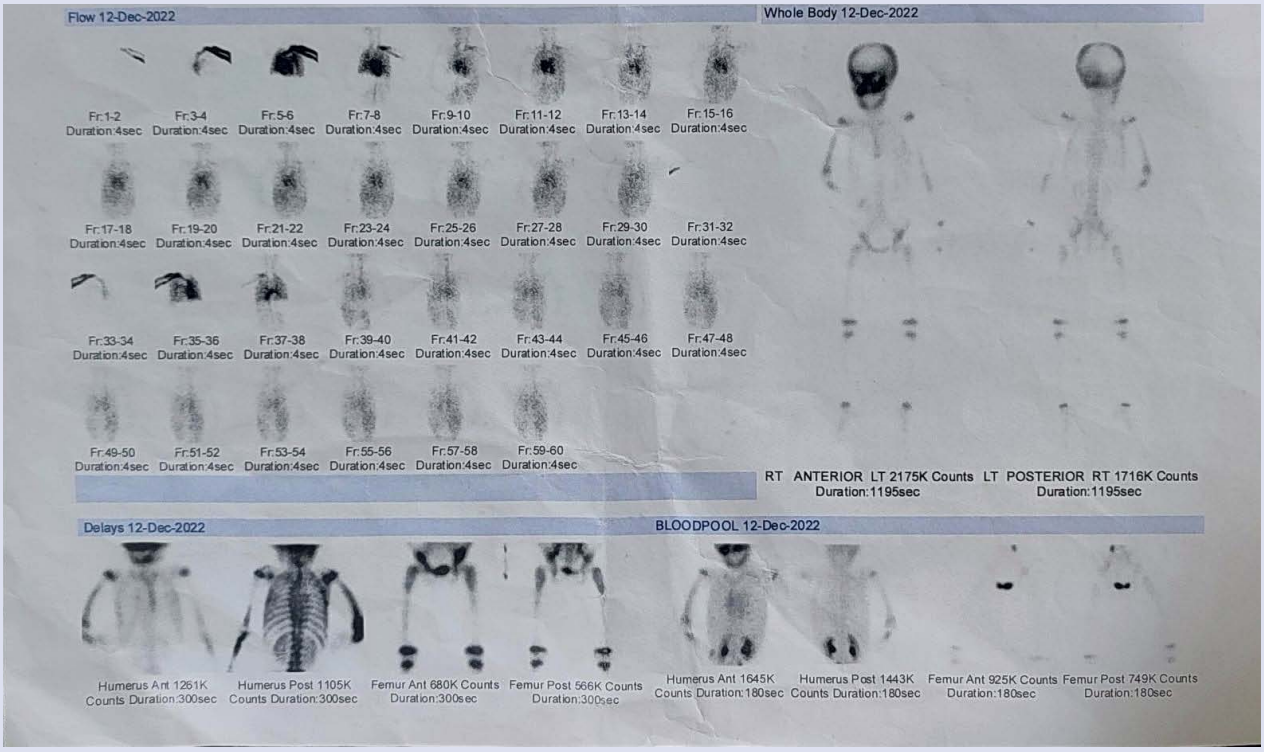


Figure 5. Dynamic bone scan findings are consistent with polyostatic fibrous dysplasia.

of the left fibula. There was also increased radioactivity in the growth plates. Nonetheless, there was no capture of pathological radioactivity in the other bones. There was no evidence of metastasis or primary bone tumor. Our findings are more consistent for polyostatic fibrous dysplasia.

Before surgery, we corrected the tachycardia with propranolol (5 mg every 8 hours). The patient received methimazole (5 mg twice daily) as anti-hyperthyroidism. We also administered tamoxifen (an estrogen receptor blocker) at 10 mg once daily. Further surgery can be performed by the orthopedic department if the tachycardia has been controlled. If the patient is already stable and can be treated as an outpatient, we recommend a zoledronic acid injection to prevent the worsening of fibrous dysplasia and decrease pain. We also arrange for further tests such as GH stimulation test, and MRI brain focusing hypothalamus and pituitary.

DISCUSSION

In our case report, a 6-year-old girl was referred to pediatric endocrinology regarding thyroid hormone test results. Thyroid hormone test results revealed low TSH levels and elevated T3. After a comprehensive examination, we found the classic triad of McCune-Albright syndrome in the patient: fibrous dysplasia affecting more than one bone, cafe au lait macules distributed in the dorsal region along the midline, and hyperfunctional endocrinopathy. Our patient presented with more than one endocrine system involved.

Precocious puberty (PP) was confirmed by a history of painless vaginal bleeding and secondary sex characteristics such as breast budding. Laboratory results also show elevated estrogen levels with suppressed FSH, suggesting the presence of GnRH-independent activity that may be induced by the ovary itself. Another hyperfunctional endocrinopathy is hyperthyroidism, which manifests as tachycardia and increased appetite that is not followed by an increase in body weight. This was confirmed by the initial laboratory results, which showed lower TSH levels and elevated T3 levels. The patient also experienced excess GH secretion, characterized by macrocephaly and linear growth acceleration. At 6 years old, she was already in the 90th percentile, higher than the MPH of the 3–50 percentile.

The location and severity of bone lesions greatly determine the clinical outcome of fibrous dysplasia (FD). The clinical spectrum is broad, encompassing isolated lesions incidentally detected as well as systemic disease. FD can either affect multiple bones (polyostotic FD), or only one bone (monostotic FD). The lesions cause pain, fractures, deformities, and functional impairment as complications.[4] In the early stages of the disease, patients may only suffer from cramping. As the lesion expands, it can damage the bone, allowing the patient to experience pain and even fractures. Although FD lesions can affect any part of the skeleton or a combination of both, they are most commonly found in the proximal femur and base of the skull.[5]

Growth hormone excess is seen in 10-20% of patients with MAS and is caused by GNAS mutations in the anterior pituitary. In most patients, high growth hormone and hyperprolactinemia are usually coexistent.[6] Growth hormone excess is associated with an increased incidence of macrocephaly, visual neuropathy, and hearing loss.[7]

Co-incidence of precocious puberty (PP) and GH excess in McCune-Albright syndrome (MAS) is quite rare; there are only a small number of case reports of co-occurrence of GH excess and PP in MAS so far. When PP is present, it can be difficult to diagnose and treat GH excess because both PP and GH excess present with accelerated linear growth. As a result, it is possible to miss the diagnosis of GH. Therefore, considering the appropriate treatment for GH excess and PP in MAS is crucial for children and adolescents to achieve normal adult height.[8]

Although gonadal involvement is equally apparent in females and males, excessive production of sex steroids is much more common

in females.[8,9] Activation of GNAS in ovarian tissue leads to recurrent estrogen-producing cysts in nearly 85% of females. Tests showed suppressed gonadotropins along with high estradiol levels, and ultrasonography usually showed an enlarged uterus with one or more ovarian cysts. Vaginal bleeding is caused by a sudden drop in estradiol, which is associated with cyst clearance.[8] Our patient had recurrent vaginal bleeding, secondary sex characteristics, elevated estrogen levels, and lower FSH. However, based on an ultrasonographic examination, we noted only enlarged uterine size and no cysts. This condition might occur because females are often clinically asymptomatic between episodes, with normal ultrasound results and undetectable estradiol levels.[8]

In this case, our patient received tamoxifen to treat precocious puberty (PP). Children who experience uncontrolled PP may develop psychological problems, and prolonged exposure to high estrogen levels may increase the risk of endometrial cancer and breast cancer. The most established therapeutics are letrozole, a third-generation aromatase inhibitor, and tamoxifen, an estrogen receptor modulator.[10] Several studies have reported the efficacy of tamoxifen for the treatment of precocious puberty. The study conducted by Caroline and friends found that tamoxifen administration (10-20 mg/day) for 3-8 years was effective to stop vaginal bleeding and improve final height prediction in patients with MAS.[11,12] In addition, autonomous ovarian activity if left untreated may persist until adult life, which is often associated with menometrorrhagia and its effects on fertility.[9]

The majority of cases of hyperthyroidism in McCune-Albright syndrome (MAS) present in childhood and persist until adulthood. To identify subclinical hyperthyroidism all patients should undergo a history and physical examination, as well as measurement of TSH, free T4, total or free T3, and thyroid ultrasonography. In most cases measuring the ratio of T3/T4 is helpful in MAS, as hyperthyroidism is a condition that results from elevated T3 levels due to deiodinase activity. A T3/T4 ratio >20 indicates the presence of disease. Note that deiodinase activity induces the conversion of T4 to T3, caused by GNAS mutations, and results in primary T3 toxicosis[13] as seen in our patient.

We found in our patients that the severity of the disease correlated with a loss in the patient's ability to walk and function due to fractures of the bilateral femur. Hence, it is important to arrange a neuro-rehabilitation program for patients with McCune-Albright syndrome to achieve improvement in strength and range of motion. Patients may benefit from the rehabilitation program by getting more functional and suffering less dependency and morbidity.[14,15]

CONCLUSION

The diagnosis of McCune-Albright syndrome (MAS) can be done clinically. However, the delay or missed diagnosis may lead to adverse conditions. There is no specific medical treatment for patients with MAS. All medications are palliative as this is a mosaic genetic disease and requires multi-specialty collaboration. Earlier and prompt diagnosis can improve the patient's quality of life.

ACKNOWLEDGEMENTS

The authors would like to thank the staff of the Department of Child Health, Faculty of Medicine, Airlangga University for supporting this study.

FUNDING

There was no specific funding from governmental, commercial, or non-profit entities for this study.

DISCLOSURE

The authors have stated their absence of any conflict of interest regarding this study.

AUTHOR'S CONTRIBUTIONS

All authors contributed to article preparation and paper revision and have collectively assumed responsibility for all aspects of this study.

DATA AVAILABILITY

The article contains all the necessary data to support the results, no supplementary source data is needed.

REFERENCES

1. Spencer T, Pan KS, Collins MT, Boyce AM. The Clinical Spectrum of McCune-Albright Syndrome and Its Management. *Horm Res Paediatr*. 2019;92(6):347-356. doi: 10.1159/000504802.
2. Turan S, Bastepe M. GNAS Spectrum of Disorders. *Curr Osteoporos Rep*. 2015;13(3):146-58.
3. Boyce AM, Florenzano P, de Castro LF, et al. Fibrous Dysplasia / McCune-Albright Syndrome. 2015 Feb 26. In: Adam MP, Feldman J, Mirzaa GM,.., editors. GeneReviews®. Seattle (WA): University of Washington. https://www.ncbi.nlm.nih.gov/books/
4. Hartley I, Zhadina M, Collins MT, Boyce AM. Fibrous Dysplasia of Bone and McCune-Albright Syndrome: A Bench to Bedside Review. *Calcif Tissue Int*. 2019;104(5):517-529. doi: 10.1007/s00223-019-00550-z
5. Boyce AM, Collins MT. Fibrous Dysplasia/McCune-Albright Syndrome: A Rare, Mosaic Disease of Gα s Activation. Endocr Rev. 2020;41(2):345–70. doi: 10.1210/endrev/bnz011.
6. Salenave S, et al., Acromegaly and McCune-Albright syndrome. *J Clin Endocrinol Metab*. 2014;99(6):1955–69.
7. Tessaris D, Growth hormone-Insulin-like growth factor 1 axis hyperactivity on bone fibrous dysplasia in McCune-Albright Syndrome. *Clin Endocrinol (Oxf)*. 2018;89(1):56–64.
8. Zhai X, Duan L, Yao Y, Xing B, Deng K, Wang L, et al. Clinical Characteristics and Management of Patients With McCune-Albright Syndrome With GH Excess and Precocious Puberty: A Case Series and Literature Review. *Front Endocrinol (Lausanne)*. 2021;12:672394. doi: 10.3389/fendo.2021.672394.
9. Irianto KA, Dewi LGDA, Adyaksa G. Streeter Dysplasia, from Pelvic to Digits: A Case Report. *Bali Med J*. 2016;5(3):509-15. doi: 10.15562/bmj.v5i3.328.
10. Eyman A, Eugster EA. Treatment of Girls and Boys With McCune-Albright Syndrome With Precocious Puberty–Update 2017. Pediatr Endocrinol Reviews: PER. 2017;15(2):136. doi: 10.17458/per.vol15.2017.nau.treatmentgirlsb.
11. De G C, Passone B, Kuperman H, de Menezes-Filho HC, Esteves LSO, Giroto RLO, Damiani D. Tamoxifen Improves Final Height Prediction in Girls with McCune-Albright Syndrome: A Long Follow-Up. *Horm Res Paediatr*. 2015;84(3):184–189. doi: 10.1159/000435881.
12. Ika Wahyuniari IA, Nyoman Arijana IGK, Sriwidyani NP, Dewi Wiryanthini IA, Suwito H, Widyarini S, Ghufron M, Mustofa M, Mubarika S. The anticancer activity of (e)-1-(4â€™-aminophenyl)-3-phenylprop-2-en-1-on against DMBA-induced mammary cancer in Sprague Dawley rat through the regulation of microRNA-21 expression. *Bali Med J*. 2017;6(3):589-94. doi: 10.15562/bmj.v6i3.697.
13. Javaid MK, Boyce A, Appelman-Dijkstra N, Ong J, Defabianis P, Offiah A. Best practice management guidelines for fibrous dysplasia/McCune-Albright syndrome: a consensus statement from the FD/MAS international consortium. *Orphanet Journal of Rare Diseases*. 2019;14(1):139. doi: 10.1186/s13023-019-1102-9.

14. Paul SM, Gabor LR, Rudzinski S, Giovanni D, Boyce AM, Kelly MR. Disease severity and functional factors associated with walking performance in polyostotic fibrous dysplasia. *Bone*. 2014;60:41-7.

15. Martadiani ED, Asih MW, Sumadi IWJ, Putra IWGAE, Suastari NMP, Martani IP, Asih KP. Correlation between radiographic and histopathological findings of conventional osteosarcoma subtypes: osteoblastic, chondroblastic, and fibroblastic. *Bali Med J.* 2021;10(3):1093-100. doi: 10.15562/bmj.v10i3.2921.

Cite this article: Khairunnisa, Faizi M, Rochmah N, Hisbiyah Y, Perwitasari RK. A Girl with McCune-Albright Syndrome: Case Study. Pharmacogn J. 2024;16(3): 706-710.