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Case Report **Medicine**

Atypical McCune–Albright Syndrome Presenting with Growth Hormone–Mediated Gigantism Despite a Normal Pituitary MRI: A Case Report

F. Aziouaz[1]*, D. Kadan[1], M. Benkacem[1]

[1]Endocrinology, Diabetology and Metabolic Diseases Department, University Hospital of Tangier, Faculty of Medicine and Pharmacy of Tangier, Abdelmalek Essaadi University, Morocco

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***Corresponding author:** F. Aziouaz
Endocrinology, Diabetology and Metabolic Diseases Department, University Hospital of Tangier, Faculty of Medicine and Pharmacy of Tangier, Abdelmalek Essaadi University, Morocco

Abstract

Introduction: McCune–Albright syndrome (MAS) is a rare, sporadic mosaic disorder caused by postzygotic activating mutations of the GNAS gene. It is classically characterized by a triad of polyostotic fibrous dysplasia, café-au-lait skin macules, and hyperfunctioning endocrinopathies. Growth hormone (GH) excess represents a particularly challenging manifestation and is most often associated with pituitary adenomas or somatolactotroph hyperplasia. However, atypical presentations with GH excess in the absence of radiologically detectable pituitary lesions have been reported. ***Case presentation:*** We report the case of a 43-year-old male referred for progressive craniofacial deformity and excessive height. Clinical evaluation revealed features consistent with GH excess, including gigantism, frontal bossing, prognathism, and progressive respiratory and neurological complications. Imaging demonstrated extensive polyostotic fibrous dysplasia involving the craniofacial bones, thoracic cage, and spine, resulting in severe skeletal deformities and multisystem complications. Biochemical assessment confirmed GH excess with elevated insulin-like growth factor 1 levels and failure of GH suppression during an oral glucose tolerance test. Notably, pituitary magnetic resonance imaging was completely normal, with no evidence of adenoma or hyperplasia. Additional endocrine evaluation revealed hypogonadotropic hypogonadism and structural thyroid abnormalities without functional hyperthyroidism. Based on the constellation of clinical, biochemical, and imaging findings, a diagnosis of atypical McCune–Albright syndrome was established. The patient was managed medically with a long-acting somatostatin analog and multidisciplinary follow-up. ***Conclusion:*** This case highlights the marked phenotypic heterogeneity of McCune–Albright syndrome and underscores that growth hormone–mediated gigantism may occur despite a normal pituitary MRI. Recognition of such atypical presentations is crucial to avoid diagnostic delay and to guide appropriate management. A multidisciplinary approach remains essential for optimizing outcomes in patients with complex skeletal and endocrine involvement

Keywords: McCune–Albright syndrome, Growth hormone excess, Gigantism, Polyostotic fibrous dysplasia, Normal pituitary MRI, Hypogonadotropic hypogonadism.

INTRODUCTION

McCune–Albright syndrome (MAS) is a rare, sporadic disorder classically defined by a triad of polyostotic fibrous dysplasia, café-au-lait skin macules, and hyperfunctioning endocrinopathies, most commonly precocious puberty, hyperthyroidism, and growth hormone (GH) excess [1,2]. The disorder results from postzygotic somatic activating mutations in the GNAS gene, which encodes the stimulatory G protein alpha subunit (Gsα). These mutations lead to constitutive activation of adenylate cyclase, persistent elevation of intracellular cyclic adenosine monophosphate (cAMP) levels, and autonomous hormonal hypersecretion in affected tissues [3-6].

Because GNAS mutations occur postzygotically, MAS is characterized by marked phenotypic heterogeneity. The clinical spectrum depends on the degree of mosaicism and the distribution of mutant cells among tissues, resulting in highly variable skeletal, cutaneous, and endocrine manifestations [7,8]. The estimated prevalence of MAS ranges from 1 in 100,000 to 1 in 1,000,000 individuals, highlighting the rarity of this condition [9].

Endocrine involvement in MAS is heterogeneous and may affect one or multiple glands. Growth hormone excess represents one of the most challenging manifestations due to its insidious onset and its contribution to significant morbidity, including craniofacial deformities, neurological complications, and cardiovascular involvement [10,11]. In most cases, GH excess in MAS is associated with pituitary adenomas or somatolactotroph hyperplasia. However, atypical presentations have been reported in which GH-mediated gigantism occurs in the absence of radiologically detectable pituitary lesions, underscoring the diagnostic complexity and broad phenotypic variability of the syndrome [12,13,14,15].

Herein, we report an atypical case of McCune–Albright syndrome in an adult male presenting with growth hormone–mediated gigantism and a completely normal pituitary magnetic resonance imaging (MRI). This case further illustrates the diverse clinical spectrum of MAS and emphasizes that the absence of pituitary abnormalities on imaging does not exclude clinically significant GH excess in affected patients.

CASE PRESENTATION

A 43-year-old male was referred to the Endocrinology Department of Tangier University Hospital for evaluation of progressive craniofacial deformity associated with excessive height, which had significantly impaired his quality of life (Figure 1).

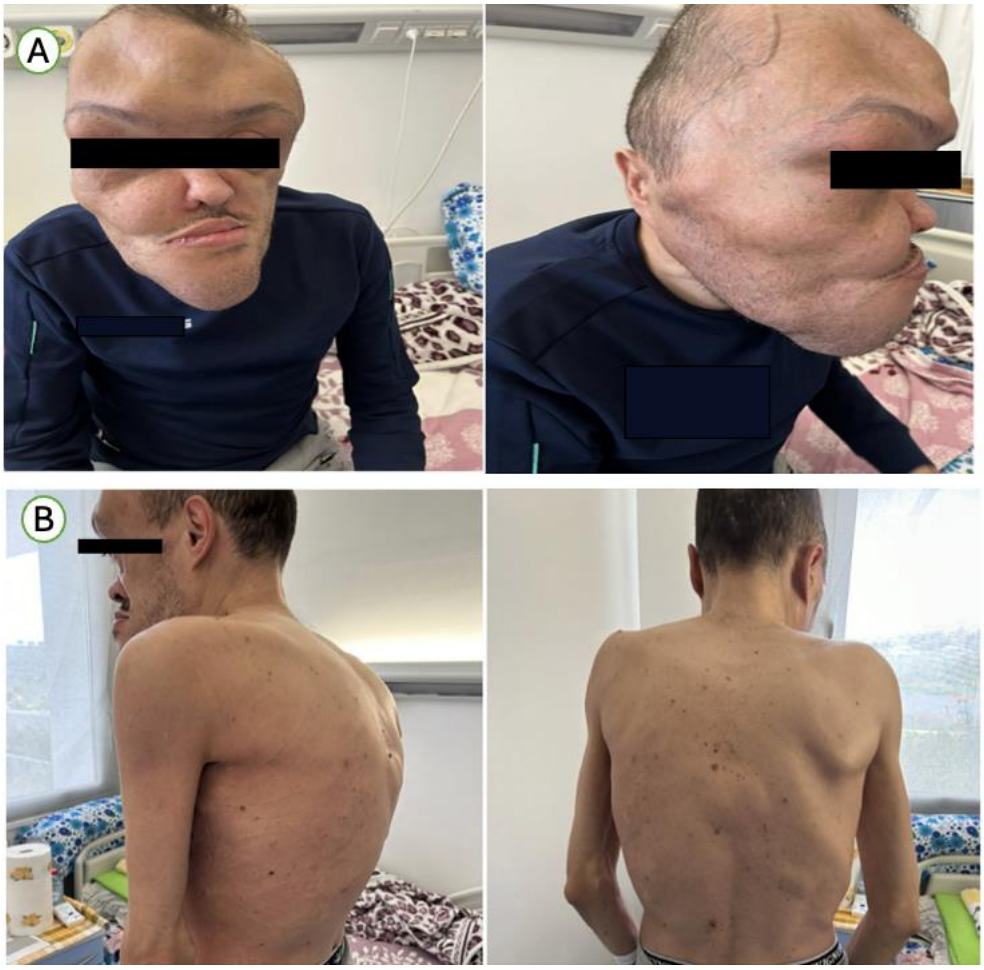

Figure 1: Adult clinical features illustrating craniofacial deformities in frontal and lateral views (A) and thoracic cage deformities in frontal and lateral views (B) in a patient with McCune–Albright syndrome

He was born at term following an uncomplicated pregnancy and delivery. There was no family history of endocrinopathies, no parental consanguinity, and no history of prior surgery. He denied exposure to chronic medications and reported no history suggestive of precocious puberty. A childhood photograph documented a normal craniofacial appearance prior to the development of clinical manifestations (Figure 2).

Figure 2: Childhood photograph of the patient showing a normal craniofacial appearance prior to the development of clinical manifestations of McCune–Albright syndrome

At the age of 7 years, the patient noticed the gradual appearance of a painless right-sided submucosal mass in the oral cavity, which progressively increased in size and eventually interfered with speech and mastication. This lesion was associated with ipsilateral craniofacial deformity. During late adolescence, at approximately 18 years of age, progressive deformities of the trunk and thoracic cage became evident. Around the same period, the patient noted that he was significantly taller than his peers. Additional symptoms suggestive of growth hormone excess progressively developed, including deepening of the voice, an increase in shoe size over recent years, excessive nocturnal snoring, and progressive exertional dyspnea.

The clinical course was further complicated by progressive vision loss in the right eye and ipsilateral hearing impairment. Otologic examination supported conductive hearing loss based on Rinne and Weber tests; however, the patient declined formal audiometric evaluation due to financial constraints. Fundoscopic examination revealed pallor of the right optic disc, while the left eye demonstrated normal retinal structures.

At admission, the patient also reported chronic dyspnea and severe pleuritic chest pain. Chest radiography demonstrated a left-sided pleural effusion. Pleural biopsy revealed a hemorrhagic effusion consistent with hemothorax of undetermined origin. In the endemic context, tuberculosis was investigated, with both GeneXpert and QuantiFERON tests yielding negative results. Further evaluation with whole-body computed tomography (CT) revealed extensive polyostotic fibrous dysplasia involving multiple axial and appendicular bones, including the ribs and thoracic cage. These skeletal lesions were associated with recurrent hemothorax requiring repeated drainage by the cardiothoracic surgery team. The chronic mass effect resulted in displacement of mediastinal structures toward the right, reduction of right lung volume, and secondary pulmonary hypertension. Spirometry demonstrated a restrictive ventilatory pattern with a forced expiratory volume in one second (FEV_1) of 1.33 L and a forced vital capacity (FVC) of 1.83 L.

Cranial CT imaging showed extensive fibrous dysplasia of the craniofacial bones, predominantly affecting the right side, with optic canal narrowing consistent with the observed visual loss. Additional skeletal involvement included axial and appendicular bones, complicated by multiple vertebral fractures at different levels of the thoracic and lumbar spine, resulting in kyphosis and scoliosis.

At 42 years of age, the patient developed progressive paresthesia and numbness of the lower limbs, followed by bilateral lower-limb weakness. Spinal CT imaging demonstrated fibrous dysplasia involving thoracic and lumbar vertebrae with spinal canal stenosis and compression of the spinal cord and nerve roots.

Notably, the patient reported no history of bone pain throughout his life, despite the extensive skeletal involvement documented on imaging.

On physical examination, the patient was hemodynamically stable. Measured height was 188 cm; however, this was underestimated due to severe spinal deformities. After correction for kyphoscoliosis, his estimated height was approximately 191 cm, exceeding the 95th percentile for adult males. General examination revealed marked craniofacial asymmetry with predominant right-sided involvement, a right-sided oral submucosal mass, and external strabismus of the right

eye. Visual field testing confirmed complete blindness in the right eye with preserved vision in the left eye. Clinical features suggestive of growth hormone excess included frontal bossing, prominent supraorbital ridges, prognathism, and tall stature. No café-au-lait macules were identified.

Cardiopulmonary examination demonstrated severe thoracic cage deformity with mixed kyphosis and scoliosis. Cardiac auscultation revealed rightward displacement of heart sounds without murmurs. Pulmonary examination showed absent breath sounds and dullness to percussion over the lateral thoracic region. Transthoracic echocardiography confirmed rightward displacement of the heart, concentric left ventricular hypertrophy with preserved systolic function, and moderate pulmonary hypertension with an estimated pulmonary artery pressure of 50 mmHg.

Abdominal examination was unremarkable. Neurological examination revealed preserved cranial nerve function except for the previously described visual and auditory deficits. Motor and sensory examination of the limbs was largely intact, with reduced lower-limb muscle strength attributed to spinal deformity.

Examination of the external genitalia revealed marked scrotal enlargement with testes of normal volume (Tanner stage V). The patient reported erectile and ejaculatory dysfunction. Hormonal evaluation demonstrated hypogonadotropic hypogonadism (LH 1.47 mIU/mL, FSH 4.62 mIU/mL, total testosterone 2 ng/mL). Tumor markers were within normal limits (α-fetoprotein 1.2 U/mL, reference <5.8; β-hCG 5.5 mIU/mL, reference <5). Testicular ultrasound and magnetic resonance imaging (MRI) showed normal testicular size and vascularization, bilateral testicular microcalcifications, and bilateral hydroceles without focal lesions.

Biochemical evaluation revealed elevated insulin-like growth factor 1 (IGF-1) at 347 ng/mL (1.2 times the upper limit of normal). An oral glucose tolerance test demonstrated failure of growth hormone suppression, with a nadir GH level of 42.36 ng/mL at 60 minutes. Pituitary MRI showed no evidence of adenoma or pituitary hyperplasia. Evaluation of the remaining pituitary axes was unremarkable.

Adrenal function was normal, with a morning cortisol level of 14 µg/dL and a 24-hour urinary free cortisol of 69 µg/24 h (reference 8–176 µg/24 h). Thyroid function tests were within normal limits (TSH 1.31 µIU/mL, free T4 15.8 pmol/L). Thyroid ultrasound identified two right-lobe nodules measuring 13 mm each, classified as EU-TIRADS 3. Serum calcitonin, calcium, and parathyroid hormone levels were normal.

Based on the combination of growth hormone excess, extensive polyostotic fibrous dysplasia, and associated endocrine and skeletal findings, a clinical diagnosis of McCune–Albright syndrome was established. The patient was discharged with a multidisciplinary follow-up plan involving endocrinology, orthopedics, cardiothoracic surgery, and neurology. Medical treatment with a long-acting somatostatin analog (lanreotide 120 mg every 28 days) was initiated, along with vitamin D supplementation. Scheduled follow-up included reassessment of IGF-1 and GH levels after three months, monitoring of metabolic parameters, surveillance of thyroid nodules, and ongoing orthopedic and neurological evaluation.

DISCUSSION

McCune–Albright syndrome (MAS) is a rare, sporadic mosaic disorder caused by postzygotic activating mutations of the GNAS gene, leading to constitutive activation of the Gsα protein and chronic intracellular cAMP signaling [1]. This molecular mechanism accounts for the heterogeneous clinical spectrum of MAS, which includes skeletal lesions, endocrine hyperfunction, and a wide range of extra-endocrine manifestations. The present case illustrates an atypical and severe adult presentation of MAS, characterized by extensive polyostotic fibrous dysplasia and growth hormone (GH)–mediated gigantism in the absence of detectable pituitary abnormalities on magnetic resonance imaging.

Fibrous dysplasia represents the skeletal hallmark of MAS and results from impaired differentiation of skeletal stem cells driven by GNAS activation [1]. Lesions typically emerge in early childhood, progress during growth, and may stabilize after puberty. Craniofacial bones, ribs, pelvis, and long bones are most frequently involved, leading to deformities, fractures, and neurological complications due to nerve compression [1,13]. In the present case, fibrous dysplasia was remarkably extensive, affecting both axial and appendicular skeleton, with severe craniofacial involvement, vertebral fractures, spinal deformities, and thoracic cage distortion. These skeletal abnormalities resulted in significant complications, including optic canal stenosis with unilateral blindness, conductive hearing loss, recurrent hemothorax, restrictive lung disease, and secondary pulmonary hypertension. Notably, despite this extensive skeletal burden, the patient reported no history of bone pain, which is unusual in polyostotic fibrous dysplasia and further highlights the phenotypic variability of MAS.

Endocrine involvement in MAS is heterogeneous and may affect multiple glands, with GH excess occurring in approximately 10–20% of patients [9,18,19]. GH hypersecretion in MAS is typically attributed to pituitary somatolactotroph hyperplasia or adenomas, although the underlying mechanism is distinct from sporadic acromegaly. In contrast to non-MAS-related acromegaly, pituitary lesions in MAS are often difficult to visualize, and surgical management is

frequently contraindicated due to skull base thickening and highly vascularized dysplastic bone [1,9]. Importantly, radiological evidence of pituitary adenoma is present in less than half of MAS patients with GH excess, emphasizing that a normal pituitary MRI does not exclude clinically significant GH hypersecretion [13,14,19].

The present case exemplifies this diagnostic challenge. Despite clear clinical and biochemical evidence of GH excess—manifested by gigantism, elevated IGF-1 levels, and failure of GH suppression during oral glucose tolerance testing—pituitary MRI was completely normal, with no evidence of adenoma or hyperplasia. This finding supports the concept that GH hypersecretion in MAS may occur through diffuse or microscopic pituitary involvement below the resolution of conventional imaging, or through functional dysregulation without macroscopic structural change. Clinically, GH excess in this patient likely contributed to the progression of craniofacial deformities, visual and auditory impairment, and possibly spinal canal stenosis through soft tissue hypertrophy, compounding the skeletal effects of fibrous dysplasia.

Medical therapy remains the cornerstone of treatment for GH excess in MAS. Long-acting somatostatin analogs and GH receptor antagonists, either alone or in combination, have demonstrated efficacy in achieving biochemical control in most patients [1,9,18,19]. In this case, medical management with a long-acting somatostatin analog was initiated, in accordance with current recommendations, given the absence of a surgical target and the high operative risk associated with craniofacial fibrous dysplasia.

Gonadal involvement is common in MAS, particularly in males, where testicular lesions are frequently detected on imaging [13,20]. While most affected boys exhibit structural testicular abnormalities, only a minority develop autonomous testosterone secretion leading to gonadotropin-independent precocious puberty. In contrast, the present patient demonstrated hypogonadotropic hypogonadism, an uncommon endocrine finding in MAS. This may reflect pituitary dysfunction related to chronic GH excess or compressive and functional alterations of the hypothalamic–pituitary axis, further underscoring the complexity of endocrine regulation in MAS.

Thyroid involvement is another recognized manifestation of MAS, ranging from structural abnormalities to overt hyperthyroidism [1,2,5]. In this case, thyroid nodules were identified in the absence of biochemical hyperthyroidism, illustrating partial gland involvement without functional autonomy. Other endocrine axes, including adrenal and parathyroid function, were preserved, highlighting the mosaic and selective nature of GNAS mutation expression.

Cutaneous café-au-lait macules are a classical feature of MAS and often provide an early diagnostic clue. However, their absence does not exclude the diagnosis, particularly in adults with predominant skeletal and endocrine involvement. The lack of café-au-lait macules in this patient further emphasizes the broad phenotypic spectrum of MAS and reinforces the importance of considering this diagnosis even when classical features are incomplete.

Beyond endocrine and skeletal involvement, MAS may affect multiple organ systems, including the cardiovascular and hepatobiliary systems [21,22,23]. Cardiovascular manifestations are thought to arise from direct involvement of cardiac tissue carrying the GNAS mutation, leading to myocardial hypertrophy and cardiomegaly. In the present case, cardiac involvement was likely multifactorial, related to thoracic deformity, pulmonary hypertension, and possible direct myocardial effects, reinforcing the need for comprehensive, multidisciplinary evaluation.

Overall, this case highlights the extreme phenotypic heterogeneity of McCune–Albright syndrome and underscores several important clinical messages: first, GH excess may occur in MAS even in the absence of detectable pituitary lesions; second, severe fibrous dysplasia can lead to life-threatening complications beyond bone pain and deformity; and third, a multidisciplinary approach is essential for optimal management of these complex patients. Recognition of atypical presentations is crucial to avoid diagnostic delay and to initiate appropriate long-term surveillance and treatment.

CONCLUSION

This case highlights the marked phenotypic heterogeneity of McCune–Albright syndrome and underscores the diagnostic challenges posed by atypical presentations. Growth hormone–mediated gigantism may occur in MAS despite the absence of radiologically detectable pituitary lesions, emphasizing that a normal pituitary MRI does not exclude clinically significant GH excess. Extensive polyostotic fibrous dysplasia can lead to severe multisystem complications, including neurological, respiratory, and cardiovascular involvement, even in the absence of bone pain or classic cutaneous manifestations. This report reinforces the importance of maintaining a high index of suspicion for MAS in patients with complex skeletal and endocrine abnormalities and supports a multidisciplinary, individualized approach to diagnosis, management, and long-term follow-up.

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