Role of dental clinical and imaging exam during McCune Albright Syndrome diagnosis process: Case Report

Importância do exame clínico e imaginológico odontológico durante o processo diagnóstico da Síndrome de McCune Albright: Relato de Caso

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Felipe Herbert de Oliveira Mendes
Graduando em Odontologia
Instituição: Centro Universitário Christus (UNICHRISTUS)
Endereço: Rua João Adolfo Gurgel, 133, Cocó, Fortaleza-CE, Brasil
Email: felipehom@hotmail.com

Thiago Jonathan Silva dos Santos
Residente em Cirurgia Bucomaxilofacial do Hospital Universitário Walter Cantídio
Instituição: Universidade Federal do Rio Grande do Norte- UFRN
Endereço: Rua Monsenhor Furtado, S/N, Rodolfo Teófilo, Fortaleza-CE, Brasil
Email: thiagojonath@outlook.com

Jéssica Emanuella Rocha Paz
Residente em Cirurgia Bucomaxilofacial do Hospital Universitário Walter Cantídio
Instituição: Centro Universitário Uninovafapi
Endereço: Rua Monsenhor Furtado, S/N, Rodolfo Teófilo, Fortaleza-CE, Brasil
Email: jessicapazctbmf@outlook.com

Ícaro Girão Evangelista
Residente em Cirurgia Bucomaxilofacial do Hospital Universitário Walter Cantídio
Instituição: Universidade de Fortaleza- UNIFOR
Endereço: Rua Monsenhor Furtado, S/N, Rodolfo Teófilo, Fortaleza-CE, Brasil
Email: icarogirao8@gmail.com

Francisco Samuel Rodrigues Carvalho
Professor Adjunto da Universidade Federal do Ceará Campus Sobral
Instituição: Universidade Federal do Ceará- UFC
Endereço: Rua Monsenhor Furtado, 1273, Rodolfo Teófilo, Fortaleza-CE, Brasil
Email: samuelrcarvalho@gmail.com

Ana Paula Negreiros Nunes Alves
Professora Associada da Universidade Federal do Ceará
Instituição: Universidade Federal do Ceará- UFC
Endereço: Rua Monsenhor Furtado, 1273, Rodolfo Teófilo, Fortaleza-CE, Brasil
Email: ananegreiroalves@gmail.com
Eduardo Costa Studart Soares  
Professor Titular da Universidade Federal do Ceará  
Instituição: Universidade Federal do Ceará - UFC  
Endereço: Rua Monsenhor Furtado, 1273, Rodolfo Teófilo, Fortaleza-CE, Brasil  
Email: estudart@yahoo.com.br

Fábio Wildson Gurgel Costa  
Professor Adjunto da Universidade Federal do Ceará  
Instituição: Universidade Federal do Ceará - UFC  
Endereço: Rua Alexandre Baraúna, 949, Rodolfo Teófilo, Fortaleza-CE, Brasil  
Email: fwildson@yahoo.com.br

**ABSTRACT**

McCune Albright Syndrome (MAS) is a rare disease characterized by the classic triad of early puberty that begins in the embryonic period and mainly affects women. The present study aims to report the case of a 27-year-old patient, melanodermic, referred to the oral and maxillofacial surgery service of the Walter Cantídio University Hospital, complaining of pain in the right mandibular body region. During the anamnesis, the patient reported having had her menarche at the age of 6. Clinically, it was observed body asymmetry, prominence of the right zygomatic, frontal and parietal bones, and expansion of the right hemimandible. Panoramic radiography showed images with ground-glass appearance in the region of the direct hemi-mandible with mixed radiopacity and root resorption, suggestive of MAS. The patient was referred to the gynecologist and endocrinologist, and it was observed that the patient had the presence of cyst in the right ovary. Incisional biopsy was performed on the right maxilla, which showed histopathological characteristics compatible with fibrous dysplasia, with final diagnosis of MAS. In summary, the present study reinforces the importance of a meticulous and interdisciplinary clinical examination allied to the patient’s complaint in order to establish an adequate treatment plan.

**Keywords:** McCune Albright Syndrome, craniofacial complex, diagnosis process.

**RESUMO**

A Síndrome de McCune Albright (SMA) é uma doença rara caracterizada pela tríade clássica da puberdade precoce que começa no período embrionário e afeta principalmente as mulheres. O presente estudo tem como objetivo relatar o caso de uma paciente de 27 anos, melanodérmica, encaminhada ao serviço de cirurgia oral e maxilofacial do Hospital Universitário Walter Cantidium, com queixa de dor na região do corpo mandibular direito. Durante a anamnese, a paciente relatou ter menarca aos 6 anos de idade. Clinicamente, observou-se assimetria corporal, proeminência dos ossos zigomáticos, frontais e parietais direitos e expansão da hemi-mandíbula direita. A radiografia panorâmica mostrou imagens com aparência de vidro fosco na região da hemi-mandíbula direita com radiopacidade mista e reabsorção radicular, sugestivas de SMA. O paciente foi encaminhado ao ginecologista e endocrinologista, e observou-se que o paciente apresentava cisto no ovário direito. Foi realizada biópsia incisional na maxila direita, que
apresentava características histopatológicas compatíveis com displasia fibrosa, com diagnóstico final de SMA. Em resumo, o presente estudo reforça a importância de um exame clínico meticuloso e interdisciplinar aliado à queixa do paciente, a fim de estabelecer um plano de tratamento adequado.

**Palavras-Chave:** Síndrome de McCune Albright, complexo craniofacial, processo diagnóstico.

**1 INTRODUCTION**

Initially described in 1937 by Donovan James McCune and Fuller Albright, McCune Albright Syndrome (SMA) is a rare disease characterized by the classic triad of early puberty: café au lait macules and polyostotic bone fibrous dysplasia (1). SMA is caused by a rare GNAS gene disorder caused by a sporadic G-protein-specific post-zygotic somatic mutation, causing excessive production of the cAMP intracellular flag. The activation of G protein is associated with the origin of endocrinopathies pertinent to AMS, and its state of activation or inactivation includes, in the skin, the macula "café au lait"; in the ovary, the presence of early puberty and, in the bone, the fibrous dysplasia pathology (2-4). Because it occurs only in the mosaic state during the embryogenesis period, the syndrome presents a distribution of clinical manifestations, ranging from multisystemic disease to involvement of a single organ (5).

Clinically, SMA is most commonly observed in females, and symptoms usually appear in childhood (5). Clinical symptoms range from autonomous endocrine hyperfunctions such as Cushing syndrome, hyperthyroidism, occult thyrotoxicosis, hyperprolactinemia, excess growth hormone (GH) and ovarian cysts to non-endocrine disorders such as cardiac dysfunction, hepatitis, gastrointestinal polyps and cholestasis (6). At imaging, fibrous dysplasia usually presents a "frosted glass" or "ground-glass" appearance, resulting from the superimposition of a myriad of poorly calcified, disorganized bone trabeculae. It is worth mentioning that these characteristics are not the rule and are directly related to the degree of development of the lesion. By histologically analyzing, it is possible to observe complex alterations evidencing the absence of continuity of bone trabeculae for the presence of a fibrous stroma, including star-shaped osteoblasts, sharpey fibers and excess osteoid tissue with indicative of submineralization (7). In general, McCune Albright syndrome is a variant of fibrous dysplasia, with neurofibromatosis, osteofibrous dysplasia and non-ossifying fibromas as the differential diagnosis, with classical triad and genetic counseling as indicative for the diagnosis of AMS (8,9). In circumstances in which there is an increase in bone volume in the jaws,
with the need for surgical approach, the most commonly approached technique is osteoplasty and/or surgical excision, while, pharmacologically, somatostatin analogs and bisphosphonates are used when necessary (10).

Diagnosis is classically defined when at least two of the main typical characteristics are present. Other diseases may also be associated with Acromegaly, affecting 20 to 30% of patients with AMS, which is more frequent in males. In females, in addition to early puberty that affects about 80% of patients (11), a striking feature and little addressed in the literature of SMA is the presence of recurrent ovarian cysts that result in episodes of estrogen production and intermittent vaginal bleeding (12).

In this context, the present article aims to discuss a clinical case of a patient with clinical manifestations of AMS.

2 CASE REPORT

A 27-year-old female patient was seen at the oral and maxillofacial surgery service of the Walter Cantídio University Hospital, Brazil, complaining of mild pain in the mandibular body on the right side. The patient reported that the pain started soon after the extraction of the first right mandibular molar (46), affected by extensive dental caries. In her medical history, the patient reported that she had only undergone a surgical procedure on her right leg and that her menarche had been at 6 years of age. On extraoral clinical examination, it was observed that the patient has short stature, body asymmetry, prominence of the right zygomatic, frontal and parietal bones, and expansion of the right hemimandible. On intraoral clinical examination, the patient had no dental malocclusion, and no signs of inflammation or infection were found.

Imaging studies were requested that revealed increased bone density of the facial bones, projection of frontal and parietal bones, radiopaque area in the right mastoid bone, diffuse radiopacity in the right maxilla, presenting a "ground glass" aspect, loss of definition in the periodontal ligament of the teeth involved and altered morphology of the right hemimandible that had radiopacity mixed with root resorption in several teeth in the right posterior region (Figure 1). These results were consistent with the clinical and imaging diagnosis of fibrous dysplasia. In order to investigate a possible syndrome, the patient was asked about her childhood development and reported that she had her menarche at 6 years of age and that the right side of the foot was shorter than the left side.

The patient was referred to a gynecologist and endocrinologist for evaluation of the endocrine glands and investigation of the entire body by bone scintigraphy (figure 2). It
was found that the patient had high diffuse radioisotope intake on the right side of the body with increased bone metabolism and endocrinopathies with hormonal changes in her ovary (figure 3). Incisional biopsy was performed on the right maxilla, which showed histopathological characteristics compatible with fibrous dysplasia (Figure 4). So, the final diagnosis was SMA. Currently, the patient is returning periodically for dental follow-up and medical appointments.

3 DISCUSSION

The SMA is characterized by the presence of at least two characteristics of the classical triad: endocrinopathies, macules "café au lait" and fibrous dysplasia (FD) (13). Hyperpigmentation of café au lait in SAM is commonly observed at birth, with irregular edges characteristic of "Coasts of Maine" with a pattern of distribution that begins or ends at the midline. This pattern is associated with individuals who had the embryonic cells affected early (14). In the present report, the patient presented endocrinopathy, polyostotic fibrous dysplasia and skeletal involvement of the right leg. Kabali and collaborators, 2019, addressed two cases of manifestations of AMS without endocrine repercussion, showing that due to the existence of a molecular pathophysiology (GNAS1), there is an inconsistency in the clinical characteristics and severity of the disease in different individuals (15).

In AMS, FD is a relatively rare lesion in the craniofacial region, affected by 20%, and the involvement of frontal, sphenoid, nasoethmoid and maxillary bones may result in nasal obstruction, sinus obliteration, mainly of the frontal and maxillary sinuses, subsequently causing sinusitis (16). It is a fibro-osseous lesion characterized by a developmental hematoma, with the presence of bone and fibrous tissue, without the maturation of osteoblasts producing immature bone, newly formed and little calcified. Craniofacial bones are affected in 10 to 25% of cases in the monostotic form and in 50% of cases in the polyostotic form (17). The radiographic resource in cases of fibrous dysplasia is shown in a "ground-glass" and radiolucent pattern due to the involvement of bone mineralization (17, 18). The panoramic radiograph of the patient in this report showed an aspect of ground glass, morphological alteration of the right hemi-mandible with mixed radiopacity and root resorption of tooth 46. Magnetic resonance imaging may help in the evaluation of the involvement of cranial nerves and soft tissue structures adjacent to the lesion (16), while bone scintigraphy is generally recommended to rule out the polyostotic variable of FD (18-20).
Early puberty, independent of gonadotropin, is a characteristic frequently present in girls with AMS, affecting approximately 85% of them. Girls develop recurrent ovarian cysts, leading to the production of intermittent autonomous estrogen that can lead to vaginal bleeding with declining estrogen levels. Transvaginal ultrasonography of the patient in this report showed the presence of the cyst in the right ovary, corroborating the findings in the literature, and the patient reported during consultations that her menarche had started at 6 years of age.

A recent research conducted by Boyce et al 2019 showed studies (18; 19-21) of female patients with AMS and the presence of ovarian cysts that presented a greater predisposition to spontaneous pregnancy, while (22) had infertility. In parts, the mechanism of infertility is probably related to anovulatory cycles resulting from autonomous ovarian activity (22,23). In SMA, genetic and molecular mechanisms are caused by post-zygotic mutations in chromosome 20q13.3, resulting in the active production of G protein, which functions as a molecular switch, signaling increased production of cyclic AMP (24). Although the patient in this case report did not exhibit hypophosphatemia, a study by Collins and collaborators shows that almost 50% of patients with FD/SMA exhibit some degree of renal phosphate reduction (32). This is attributed to high levels of fibroblastic growth factor (FGF), a hormone that regulates phosphate homeostasis produced by osteoblasts and osteocytes actively involved in bone formation (25).

Akintoye and colleagues, 2013, explain that, as patients with FD grow, if there is an association with the appendicular skeleton, fractures, flaccid or skeletal pain may manifest; while in children, they manifest in fatigue and fatigue with little effort. In addition, long bones in these patients are more prone to fractures and deformities, such as the temporal femur. The patient in this report presented, in her medical history, a surgical approach to the right temporal femoral bone due to a fracture. Clinically, the correlation of FGF degree occurs with skeletal involvement and disease activity, suggesting overproduction of FGF, resulting in accumulation of active osteogenic cells in the DF lesion (26). The craniofacial region is the area most affected by polyostotic FD, with up to 87% of the patients affected and with most of the lesions developing particularly early, around 3 years of age (26, 27). The clinical presentation of FD in the craniofacial region commonly involves temporal bones (71%), followed by sphenoid bones (43%), frontal bones (33%), maxillary bones (29%), temporal bones (24%),
parietal bones (14%) and occipital bones (5%) (38). Generally, the mass is painless and slow-growing, resulting in facial asymmetry (28).

Boyce and collaborators (Boyce et al, 2018) conducted a cohort study with patients who had temporal bone FD, showing that they have an increased risk of sensorineural and conductive hearing loss (26). Fibrous Dysplasia can also manifest in the mandibular bone, causing malocclusion and dental crowding (29).

The SMA has a highly variable phenotype, and its prenatal diagnosis, even in developed countries, is challenging due to several factors, including late notification of patients, the health units where the diagnosis is reached with the help of imaging, scintigraphy and magnetic resonance imaging [29]. Dental treatment of FD/SMA is clinically complex, dependent on the degree of associated comorbidities, including endocrine disorders, skeletal load, use of bisphosphonate and general weakness. Due to malocclusion and the high rate of associated caries in patients with FD, follow-up with the dentist must be frequent in order to provide stability in the control of dental calculus accumulation [29].

Javaid et al, 2019 describe that the craniofacial surgical approach should be carefully planned, evaluating the levels of phosphate, vitamin D and endocrine abnormalities such as excess of GH and thyrotoxicosis T3 that may exacerbate the disease when altered. Thus, prior to the choice of surgical therapeutic approach, these authors cite the objectives of treatment in cases of prevention of functional loss, hearing and vision, detention or reduction of physical disfigurement, prevention of secondary deformities and minimization of long-term morbidity. Simple curettage was described as ineffective and may increase the risk of complications, while the main treatment strategy in maxilla and mandible was radical excision of the lesion. In the present case, the patient was treated conservatively because there was no aesthetic or functional complaint or signs of progression of the lesion [29, 30].

4 CONCLUSION

SMA represents a broad spectrum of associated diseases due to somatic mutations of the GNAS gene that are variable among individuals. The rarity of the disease and its multiple clinical manifestations can lead to diagnostic errors and therapeutic approaches that are not in common agreement with the needs of each patient. In short, the correct diagnosis of AMS and multidisciplinary treatment should be based on the correlation with clinical data and patient complaint, reinforcing the importance of choosing the therapeutic
approach that is in common agreement with the need of each patient to obtain a better prognosis.

Conflict of interest: The authors declare that there was no conflict of interest.

Illustrations

Figure 1.

![Figure 1](image1)

Figure 2.

![Figure 2](image2)
Figure 3.

Figure 4.
Figure 5.

Figure 6.
Figure 7.

5 FIGURE LEGENDS

Figure 1: Appearance of ground glass, morphological alteration of the right hemimandible with mixed radiopacity and root resorption.

Figure 2: Right mandibular condyle with mixed radiopacity.

Figure 3: Proximal epiphysis of the femoral bone showing mixed radiopacity.

Figure 4: Diffuse taking of the radioisotope with increased bone metabolism.

Figure 5: Transvaginal ultrasonography showing right ovary cyst.

Figure 6: Photomicrograph showing trabecular bone without osteoblast rhyme. HE, hematoxylin-eosin stain (x400).

Figure 7: Photomicrograph of bone trabeculae and osteoid material. HE, hematoxylin-eosin stain (x200).

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