CASE REPORT

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A Rare Case of McCune-Albright Syndrome in Association with Acromegaly: Treatment Options and a Review of the Literature

Akromegali ile İlişkili Nadir Bir McCune-Albright Sendromu Olgusu: Tedavi Seçenekleri ve Literatürün Gözden Geçirilmesi

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Abstract

McCune-Albright syndrome constitutes of fibrous dysplasia, café-au-lait macules, and various endocrinopathies such as thyroid, cortisol, prolactin and growth hormone hypersecretion. Growth hormone excess as a manifestation of endocrine hyperfunction is uncommon. We present a case of McCune-Albright syndrome with compressive optic neuropathy due to fibrous dysplasia and acromegaly which was resistant to different therapies. A 33-year-old male patient was admitted to our center due to loss of vision and a progressively growing mass in the right parietal region. Magnetic resonance image yielded a contrast enhanced lesion, measuring 10x15 cm in size. The patient underwent decompression surgery due to optic nerve and chiasm compression and the histopathologic evaluation was compatible with fibrous dysplasia. The patient was diagnosed with acromegaly after laboratory evaluation. Surgical treatment was not preferred. Medical therapy with octreotide LAR 10 mg once a month was recommended. Cabergoline was added to his therapy and the doses of these two medicines were gradually escalated. Pegvisomant therapy was planned because IGF-1 level was not normalized. As a rarely encountered syndrome, it is important to recognize this syndrome and evaluate for a wide range of endocrinopathies. There are various treatment options and further research is still warranted.

Keywords: Acromegaly, cabergoline, fibrous dysplasia, McCune-Albright syndrome, pegvisomant, somatostatin receptor analogues

Öz

McCune-Albright sendromu, fibröz displazi, café-au-lait lekeleri ile tiroid, kortizol, prolaktin ve büyüme hormonu hipersekresyonu gibi çeşitli endokrinopatilerden oluşur. Endokrin hiperfonksiyonunun bir belirtisi olarak büyüme hormonu fazlalığı nadirdir. Makalemizde farklı tedavilere dirençli akromegali ve fibröz displazi nedeniyle kompresif optik nöropatisi olan bir McCune-Albright sendromu olgusunu sunuyoruz. Otuz üç yaşında erkek hasta, görme kaybı ve sağ parietal bölgede giderek büyüyen kitle nedeniyle merkezimize başvurdu. Manyetik rezonans görüntülemede 10x15 cm boyutlarında kontrast tutan bir lezyon izlendi. Optik sinir ve kiazma basısı nedeniyle dekompresyon cerrahisi uygulanan olguda histopatolojik değerlendirme fibröz displazi ile uyumlu bulundu. Hastaya laboratuvar değerlendirmesinin ardından akromegali tanısı konuldu. Cerrahi tedavi tercih edilmedi. Ayda bir kez 10 mg oktreotid LAR ile medikal tedavi önerildi. Tedavisine kabergolin eklendi ve bu iki ilacın dozları yavaş yavaş artırıldı. IGF-1 düzeyi normale dönmediği için pegvisomant tedavisi planlandı. Nadir görülen bir sendrom olarak, bu sendromu tanımak ve eşlik edebilecek çeşitli endokrinopatileri değerlendirmek önem arz eder. Tedavi seçenekleri çok çeşitli olup ileri araştırmalara ihtiyaç mevcuttur.

Anahtar kelimeler: Akromegali, fibröz displazi, kabergolin, McCune-Albright sendromu, pegvisomant, somatostatin reseptör analoğu

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Introduction

Fibrous dysplasia (FD) is a congenital disease which is characterized with the replacement of medullary bone with fibrous tissue. It may cause pain, fractures and deformities in the affected bones. It presents in various clinical settings including monostotic form (solitary bone lesion), polyostotic form (multiple bone lesion), and uncommonly McCune-Albright syndrome (MAS). MAS constitutes of FD, café-au-lait macules, and different endocrinopathies such as thyroid, cortisol, prolactin (PRL) and growth hormone (GH) hypersecretion (1). GH excess as a manifestation of endocrine hyperfunction is uncommon. We presented a case of MAS with compressive optic neuropathy due to FD in association with acromegaly which was resistant to different therapies and we aimed to highlight the therapeutical challenges.

Case Report

A 33-year-old male patient was admitted to the otorhinolaryngology outpatient clinic in 2009 due to loss of vision and a progressively growing mass in the right parietal region. The mass was present since childhood. Magnetic resonance image (MRI) yielded a contrast enhanced lesion, measuring 10x15 cm in size, which invaded the sphenoid sinus, frontal sinus, and nasal cavity, compressed the cavernous sinus, displaced the clivus, extended toward optic chiasm, suprasellar region, and diploic space, expanded the midline bones (Figure 1). The patient underwent decompression surgery due to optic nerve and optic chiasm compression. The histopathologic evaluation was compatible with FD. The patient was consulted by endocrinology department with regard to associated syndromes and pituitary hormones.

He complained headache, increased sweating, and weakness. He noticed growth in hands and increase in shoe size. He was 187 cm in height and weighed 89 kg (body mass index: 25.5 kg/m^2). His blood pressure was 140/80 mmHg. His past medical history was only significant for hypertension for one year. On physical examination, prognathism, acral growth, chin asymmetry and temporal swelling were noted. Laboratory data are shown in Table 1. GH and insulin like growth hormone (IGF)-1 was elevated. Therefore, GH response during oral glucose tolerance test was evaluated. GH was not suppressed and the patient was diagnosed with acromegaly. Acromegaly along with FD was compatible with MAS. However, we did not observe any skin lesion. Skeletal survey was done. Lesions of FD were noted in the mandible, right iliac crest, acetabulum, femur head bilaterally, and proximal right tibia and fibula (Figure 2). Vertebrae were not involved. Neither osteopenia nor osteoporosis was detected on dual energy X-ray absorptiometry. Medical therapy with octreotide LAR 10 mg once a month and calcium and vitamin D supplementation were recommended. The patient was lost in the follow-up after 3 months of the treatment.

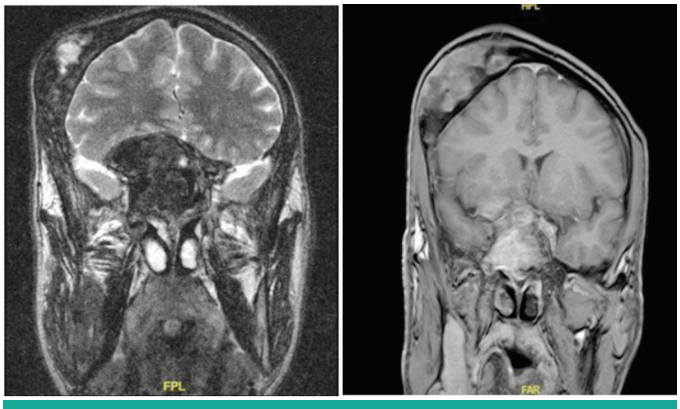

Figure 1. Magnetic resonance image of the patient

Table 1. Laboratory findings

Biochemical features	Results	Normal range
Fasting plasma glucose	79	70-110 mg/dL
Urea	33	10-50 mg/dL
Creatinine	0.8	0.6-1.3 mg/dL
Alanine transaminase	16	3-55 U/L
Aspartate transaminase	20	5-34 U/L
Sodium	140	136-145 mmol/L
Potassium	3.5	3.5-5.1 mmol/L
Calcium	9.1	8.8-10.6 mg/dL
Phosphorus	2.8	2.4-4.4 mg/dL
Parathyroid hormone	86.7	15-68.3 pg/mL
25 (OH) vitamin D	4	15-50 µg/L
Thyroid stimulating hormone	0.719	0.35-4.94 µLU/mL
Free triiodothyronine	2.9	2.6-4.3 pg/mL
Free	0.75	0.7-1.48 ng/dL
Adrenocorticotropic hormone	73.71	7.2-63.3 pg/mL
Cortisol	18	6.0-19.0 µg/dL
Follicle stimulating hormone	3.16	1.37-13.58 mLU/mL
Luteinizing hormone	2.2	0.57-12.07 mIU/mL
Total testosterone	2.25	2.4-8.7 ng/mL
Prolactin	45.26	2.58-18.12 ng/mL
Growth hormone	7.6	0.06-5.00 ng/mL
Insulin-like growth factor-1	825	115-307 ng/mL
Low dose dexamethasone suppression test	0.8	1.8 µg/dL>

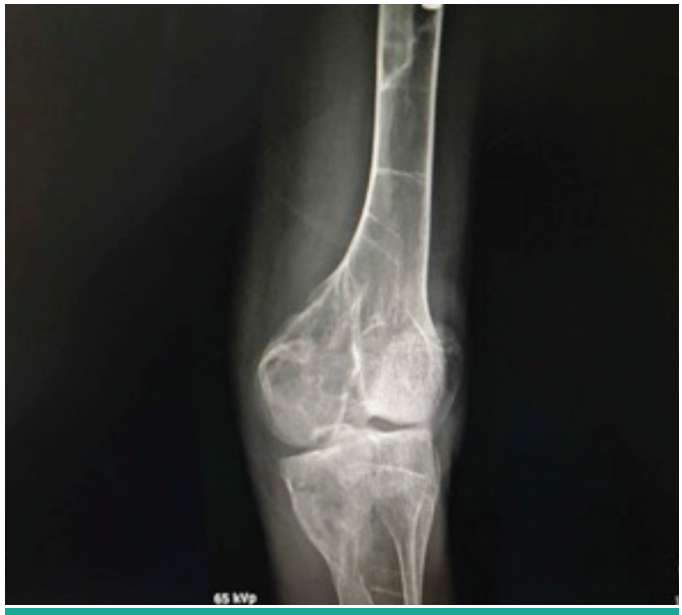

Figure 2. X-ray of the femur, tibia, and fibula

The patient was readmitted to the endocrinology unit after 2 years with the same complaints. He quitted octreotide and calcium-vitamin D in that timespan. Laboratory studies revealed GH: 6.70 ng/mL, IGF-1: 1057 ng/mL, and PRL: 42.89 ng/mL. Although thyroid function tests were within normal limits, multiple hypoechoic nodules, the largest one being 16x8 mm in size with microcalcifications, were detected on ultrasound (USG). Echocardiography revealed left atrial and ventricular enlargement, hypokinetic areas in apicolateral segments, ejection fraction of 35%. Cardiomyopathy was diagnosed. No polyps were detected on colonoscopic examination. Scrotal USG yielded normal features.

Visual field test revealed right sided temporal hemianopsy. The bone lesion was persistent on sellar MRI. Because of extensive involvement and close relation to vital structures, surgical treatment was not preferred. Therefore, octreotide 20 mg once a month was initiated again. Cabergoline 0.5 mg twice a week was added to the treatment. Octreotide dose was gradually escalated up to 40 mg and cabergoline to 1 mg twice a week. PRL level was significantly decreased. Although IGF-1 level was not normalized, it decreased significantly to 368 ng/mL. As an adverse effect of octreotide treatment, we did not detect glucose intolerance and cholelithiasis at the fifth year of therapy. Since IGF-1 level was not normalized, pegvisomant therapy was planned.

Discussion

MAS is a rare disease with an estimated prevalence of 1/100.000-1/1.000.000. Its clinical triad is composed of FD, café-au-lait skin lesions, and various endocrinopathies. It is caused by the stimulation of G protein α subunit due to activating mutations of *GNAS1* gene located on the long arm of chromosome 20 (2). The stimulation of G protein α subunits results in hyperfunctional endocrinopathies. Puberty precox is the most common endocrinopathy seen in MAS. Information regarding puberty was unclear in our patient; therefore, we could not rule out puberty precox. Although short stature is expected in puberty precox, concomitant gigantism may cover its effect on height. Other endocrinopathies constitute of acromegaly, hyperprolactinemia, hyperthyroidism, hypercortisolism, and hypophosphatemic rickets or osteomalacia. The incidence of GH excess among patients with MAS is approximately 20% (3). Chanson et al. (3) evaluated the association of acromegaly and MAS in 112 patients and they reported that the mean age at diagnosis was 24.4 (3-64) years and male was the preponderant gender (4). Our patient was diagnosed with MAS in his 30s due to the signs of GH excess and acromegaly. Acromegaly associated with MAS differs from classical acromegaly in that it is accompanied by hyperprolactinemia in 80-85% of cases and pituitary adenomas are not always detectable on imaging (2). Mechanism about discrepancy between laboratory and imaging is unclear and there are various hypotheses. A study which investigated laboratory data of 12 patients with MAS found a significant association between PRL and IGF-1 levels (5). Radiologic findings were present in 50% of MAS associated acromegaly, while the findings were present in 80% of classical acromegaly (2).

It is thought that there is no autonomy because of hypersecretion without pituitary lesion and response to somatostatin analogues. Supporting this hypothesis, mammosomatotroph hyperplasia in pituitary biopsies were shown in a study (6). A wide range of pituitary pathology may be explained by embryonic differentiation and abnormal hypothalamic regulation (7). Our case presented with elevated levels of GH, IGF-1, and PRL which decreased after cabergoline and octreotide combination therapy and absence of pituitary lesion.

Hyperthyroidism with MAS usually presents as subclinical hyperthyroidism and/or thyroid gland abnormalities on USG (8). In some cases, overt hyperthyroidism may be present, so they should be followed with thyroid function tests periodically. Although thyroid cancer is rare in MAS, considering increased malignancy risk with acromegaly, it would be judicious to monitor periodically with USG (9). Our patient was euthyroid at the time of diagnosis and

hyperthyroidism did not ensue during follow-up. Thyroid USG showed multinodular goiter. Fine needle aspiration biopsy of the suspect nodules was done and it was reported as benign. We did not observe growth in nodules.

Hypercortisolemia and adrenal hyperplasia has been reported in the literature. Cushing syndrome with MAS may undergo spontaneous remission. It is recommended to search for Cushingoid features and screen the suspected cases (10). We applied 1 mg dexamethasone suppression test to evaluate hypercortisolism and it was suppressed to less than 1.8 mcg/dL. Therefore, Cushing syndrome was ruled out.

FD is not as rare as MAS. It represents 7% of all benign bone lesions. Polyostotic involvement is evident in 30% of cases, while monostotic involvement is more common. Differentiation and abnormal proliferation of bone marrow stromal cell derived from medullary cavity give rise to FD lesions and the lesions expands exophytic masses with intact cortical bone (11). Although specific findings on imaging are generally enough for diagnosis, bone biopsy can be performed in case of indeterminant feature (1). FD in MAS mostly manifests as painless craniofacial lesions causing facial asymmetry. Cranial nerve compression, visual loss, and hearing impairment may be observed. Optic nerve may remain unaffected for years, although it is surrounded by the lesion. Ophthalmologic examination and tests for hearing loss should be done initially at diagnosis and annually thereafter (12).

Computed tomography is the most effective imaging modality for detecting craniofacial FD, but MRI is superior in detecting soft tissue and cranial nerve involvement (4). In our case, apparent craniofacial involvement caused progressive visual loss due to optic nerve compression visible on MRI scan, but hearing loss was absent. Axial and appendicular skeleton involvement may arise over time and plain films are usually enough for diagnosis (2). Vitamin D deficiency in MAS is common likewise normal population. Evaluation of vitamin D deficiency and treatment when necessary is advised.

Management of MAS is multimodal and tailored for each patient. Operation is generally ill-advised except for progressive visual and hearing loss in case of craniofacial FD (2). Transcranial surgery is the preferred method because of altered sphenoid sinus anatomy due to bone thickening. Radiotherapy has risk for sarcomatous transformation in FD, thus it is preferred only in patients who are amenable to operation and refractory to medical treatment (3). Although somatostatin receptor analogues significantly decrease GH and IGF-1 levels, remission can be achieved only in 30% of patients (13). Bromocriptin, a dopamine receptor agonist, has become a less favorable option nowadays (3). There are reports of success with combination therapy of another dopamine receptor agonist cabergoline and somatostatin receptor analogues. Akintoye et al. (5) showed good response with the use of this combination therapy in 6 out 7 patients. Combination therapy is recommended in case of inadequate control with monotherapy (5). Pegvisomant, a GH receptor antagonist, is another option in unresponsive cases (14). Our patient showed poor response to low dose octreotide and hormone levels kept increasing under therapy with intermediate dose of octreotide and cabergoline. We considered the addition of pegvisomant.

In conclusion, as a rarely encountered syndrome, it is important to recognize MAS and evaluate for a wide range of endocrinopathies in addition to lesions of FD. There are various treatment options and further research is still warranted.

Ethics

Informed Consent: Written informed consent received from the patient.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.E., Concept: H.P., O.E., Design: H.P., O.E., Data Collection or Processing: O.E., Analysis or Interpretation: H.P., Final Approval and Accountability: H.P., Writing: O.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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