

Maffucci Syndrome Associated With Adrenocorticotrophic Hormone–Independent Bilateral Macronodular Adrenal Hyperplasia

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Context: Maffucci syndrome is a rare, nonhereditary, mesodermal dysplastic disease characterized by the presence of multiple hemangiomas and enchondromas. This pathological condition, which is often unrecognized, is associated with a high prevalence of benign and malignant endocrine tumors involving pituitary, adrenal, thyroid, and parathyroid glands.

Case Description: We describe the case of a young patient presenting a history suggestive of secondary arterial hypertension and typical features of Maffucci syndrome (multiple hemangiomas and enchondromas), which were unrecognized over the previous 3 decades. Given that endocrine diseases are common causes of secondary arterial hypertension and are often associated with Maffucci syndrome, a comprehensive diagnostic workup was performed, revealing the presence of large bilateral adrenal masses (70 mm right, 35 mm left) and autonomous cortisol secretion (adrenocorticotrophic hormone–independent Cushing syndrome). The patient underwent a bilateral adrenalectomy, and steroid replacement therapy was initiated. Surgery resulted in a normalization of arterial blood pressure, and antihypertensive treatment was discontinued. Histological examinations revealed morphological features of primary bilateral macronodular adrenal hyperplasia.

Conclusions: Early recognition and lifelong monitoring of Maffucci syndrome is required to identify and treat possible associated endocrine diseases and malignancies. Among them, unilateral cortical adrenal masses have been previously described, but to our knowledge, this is the first reported case of Maffucci syndrome associated with primary bilateral macronodular adrenal hyperplasia. Additional studies are needed to establish the etiopathological link between these 2 entities and, more in general, between Maffucci syndrome and endocrine diseases, but possible common genetic alterations may be suggested.

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Freeform/Key Words: Maffucci syndrome, primary bilateral macronodular adrenal hyperplasia, Cushing syndrome, secondary arterial hypertension

Arterial hypertension is one of the leading causes of morbidity in Western countries, affecting nearly one-fourth of the adult population of the United States [1]. Although arterial hypertension has usually no clear cause (primary or essential hypertension), a specific, potentially reversible mechanism leading to blood pressure elevation can be identified in ~5% to 10% of patients (secondary hypertension) [2]. Common causes of secondary hypertension are

Abbreviations: FH, fumarate hydratase; IDH, isocitrate dehydrogenase; PBMAH, primary bilateral macronodular adrenal hyperplasia

renal and vascular disorders as well as endocrine diseases [2]. Identifying and treating the cause of elevated blood pressure is of obvious clinical importance since it may provide a cure for patients with secondary hypertension. Furthermore, an elevated blood pressure may often represent the first clinical manifestation of an unrecognized underlying disease, including Cushing syndrome, pheochromocytoma, and primary hyperaldosteronism.

Here we describe the case of a young patient presenting a history suggestive of secondary arterial hypertension and showing typical features of Maffucci syndrome (multiple hemangiomas and enchondromas), which were unrecognized over the previous 30 years. Establishing the diagnosis of this rare, nonhereditary, mesodermal dysplastic syndrome, which is associated with a high prevalence of endocrine diseases and malignancies, prompted a comprehensive medical evaluation that revealed the presence of bilateral adrenal masses and autonomous cortisol secretion.

1. Case Presentation

A 38-year-old woman was referred to our clinic to undergo screening for secondary arterial hypertension. She had a long history of arterial hypertension inadequately controlled with ramipril 10 mg/d, as recently confirmed by a 24-hour ambulatory blood pressure monitoring (156/92 mm Hg). Family and personal history were negative for risk factors and other known medical disorders. On physical examination, she had several small, compressible, painless, bluish cutaneous nodules on the right hand, wrist, forearm, and shoulder, which had appeared over the past 3 years and gradually increased in volume [Fig. 1(A)]. Furthermore, she had severe, atypical bone deformities of the last 2 fingers of the right hand. She reported that mild finger deviations were first noticed at age 15 years, when they were attributed to a juvenile traumatic fracture. However, bone deformities have become progressively worse over time without any obvious explanation, and they seriously limited hand function at the time of the visit. The patient underwent Doppler ultrasound and histopathological studies of the skin

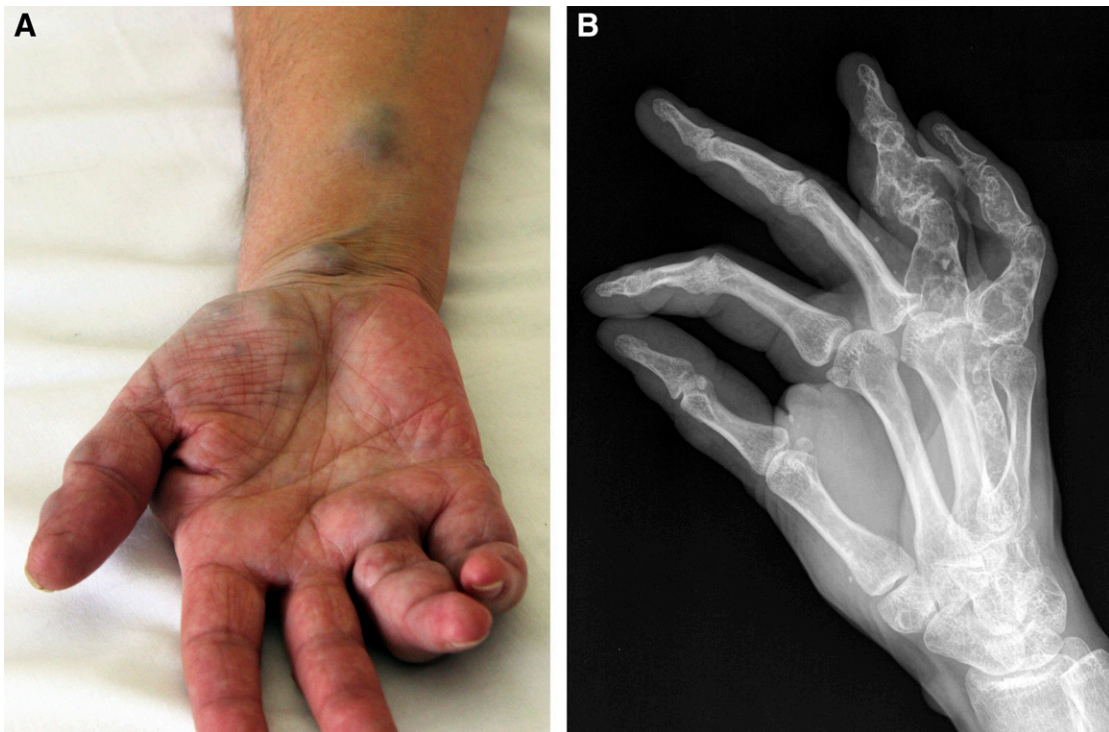


Figure 1. (A) Cavernous hemangiomas of the right hand, wrist, and forearm and (B) multiple enchondromas of the right hand.

lesions, which showed typical features of cavernous hemangiomas. In addition, a series of bone X-ray and magnetic resonance examinations revealed the presence of multiple enchondromas of her right hand [Fig. 1(B)], as well as enchondromas of the right scapula and left hand. Results from routine laboratory tests were unremarkable.

The coexistence of cutaneous hemangiomas and multiple enchondromatosis led to the diagnosis of Maffucci syndrome, a rare condition that is associated with a high prevalence of endocrine diseases and malignancies. Indeed, a comprehensive evaluation, including whole-body magnetic resonance imaging and extensive laboratory analyses, revealed the presence of large bilateral adrenal masses (70 mm right, 35 mm left) (Fig. 2) associated with autonomous cortisol secretion (plasma cortisol, 11.3 to 15.3 $\mu\text{g/dL}$; adrenocorticotropic hormone, <5 to <5 pg/mL; urinary free cortisol, 191 to 182 $\mu\text{g/d}$; absent circadian rhythm; positive 1-mg and 2-mg dexamethasone suppression tests). A diagnosis of adrenocorticotropic hormone–independent Cushing syndrome was then established. Given the patient's willingness, tumor volume, and high risk of endocrine malignancies associated with Maffucci syndrome, the patient underwent a bilateral adrenalectomy and steroid replacement therapy was initiated. Histological examinations revealed morphological features of primary bilateral macronodular adrenal hyperplasia (PBMAH). Surgery resulted in a normalization of arterial blood pressure, and antihypertensive treatment was discontinued. A long-term clinical and radiological follow-up, including annual whole-body magnetic resonance imaging, has been proposed.

2. Discussion

Maffucci syndrome is a rare, nonhereditary mesodermal dysplasia [3, 4]. Since it was first described in 1881, fewer than 200 cases have been reported worldwide [5]. It occurs in all races with equal frequency in men and women. Although the etiology of the disease remains to be confirmed, an association between Maffucci syndrome and somatic mutations in isocitrate dehydrogenase 1 (*IDH1*) or *IDH2* genes has been recently demonstrated [6, 7].

Clinically, Maffucci syndrome is characterized by the presence of soft tissue hemangiomas and multiple benign cartilaginous tumors (enchondromas) [3, 4]. Vascular and skeletal lesions are typically asymmetric, being unilateral in 50% of patients. They appear early during

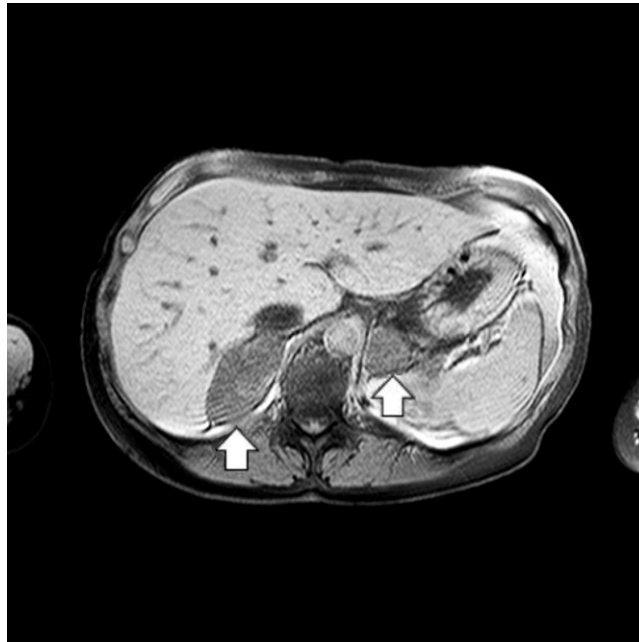


Figure 2. Abdominal magnetic resonance imaging showing the presence of large bilateral adrenal masses (70 mm right, 35 mm left).

childhood and are often progressive [3, 4]. Hemangiomas or, less frequently, lymphoangiomas manifest as compressible, painless, bluish nodules, which may be localized in superficial or deep soft tissues. Enchondromas usually affect short and long tubular bones of the extremities; in rare cases, however, they may be also present in flat bones such as pelvis, ribs, and scapulae [3, 4]. Skeletal lesions are usually asymptomatic but may lead to severe deformities and pathological fractures. Malignant transformation of enchondromas toward chondrosarcomas or hemangiomas into vascular sarcomas is a serious and frequent complication, occurring in 20% to 30% of the patients [4, 8]. An increased incidence has also been reported for other tumors, including adenomas and adenocarcinomas of pituitary, adrenal, thyroid, and parathyroid glands, as well as glioma, glioblastoma, acute myeloid leukemia, and intrahepatic cholangiocarcinomas [3, 4, 8–10].

Genetic tests have been proposed [6, 7], but the diagnosis of Maffucci syndrome mainly relies on its nearly pathognomonic clinical and radiological features. At present, there is no medical treatment for Maffucci syndrome. Surgical interventions are indicated to minimize deformities for cosmetic purposes or in case of growth defect, pathological fractures and malignant transformation [11].

The coexistence of Maffucci syndrome with unilateral cortical adrenal masses has been previously reported in two 40-year-old women showing clinical [9] or subclinical [10] features of Cushing syndrome. However, to our knowledge, this is the first reported case of Maffucci syndrome associated with bilateral cortisol-secreting adrenocortical nodules. In the general population, PBMAH represents about 10% to 15% of all incidentalomas, which in turn have a prevalence of 0.4% to 5% and a higher incidence in women than in men [12, 13]. Cushing syndrome may be observed in 35% of bilateral incidentalomas, but the diagnosis is usually insidious. Indeed, hypercortisolism typically develops gradually over several years, may be cyclical, and is frequently associated with subtle clinical manifestations, even if serious forms have been reported [12–14]. A number of genetic variants have been associated with the development of PBMAH [13, 15]. These include genes involved in cyclic adenosine monophosphate/cyclic guanosine monophosphate signaling pathways (*PDE11A*, *MC2R*, *PRKACA*, and possibly *ARMC5*) and genes associated with hereditary familial tumor syndromes (*APC*, *MEN1*, *FH*) [13, 15]. Rare variants of *PDE11A*, encoding the isoform 11A of the phosphodiesterase enzyme, may alter cyclic adenosine monophosphate degradation, leading to the upregulation of the cyclic adenosine monophosphate/protein kinase A signaling pathway, which is physiologically activated by the adrenocorticotrophic hormone. Due to the close physical proximity of *PDE11A* (2q31.2-31.3) with *IDH1* (2q33.3-34), one of the genes associated with Maffucci syndrome, we may speculate on the existence of a common genetic alteration leading to the development of both disorders. Furthermore, dysfunction of enzymes involved in the tricarboxylic acid cycle, such as fumarate hydratase (*FH*) and *IDH*, have been implicated in the pathogenesis of several malignancies, including both PBMAH and Maffucci syndrome, respectively [16]. The underlying mechanisms include a metabolic shift in favor of catabolic reactions, leading to an increased production and availability of adenosine triphosphate, an increase of reactive oxygen species, and an hyperactivation of hypoxia-inducible factor 1 α and possibly nuclear factor erythroid 2-related factor 2, which may be caused by mutations of either *FH* or *IDH* [16]. Thus, it is tempting to speculate that perturbations of the tricarboxylic acid cycle induced by the mutation of either of these enzymes may represent a common basis for oncogenesis and tumor progression of both PBMAH and Maffucci syndrome. However, because molecular studies were not performed on tumor samples, the etiopathological link between PBMAH and Maffucci syndrome remains unclear.

In conclusion, early recognition and lifelong monitoring of Maffucci syndrome are required to identify and treat possible associated endocrine diseases and malignancies in a timely fashion. Similarly, although current clinical practice discourages an elaborate workup in the general hypertensive population, this case report underlines the need for establishing the correct diagnosis and always excluding endocrine diseases in all patients with clinical suspicion of secondary arterial hypertension.

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