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MAFFUCCI' S SYNDROME COMPLICATED BY INTRACRANIAL CHONDROSARCOMA

Two new illustrative cases

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ABSTRACT - Maffucci's syndrome is a rare congenital condition, sometimes misdiagnosed as Ollier's disease, characterized by multiple enchondromas combined with hemangiomas and phlebectasia. Coexisting primary malignancies have been described sporadically. We report two cases of Maffucci's syndrome associated with cranial base chondrosarcoma, emphasizing pathophysiological features and the challenging management of intracranial chondrosarcomas. To the best of our knowledge, only twelve similar cases have been reported in the literature.

KEY WORDS: Maffucci' s syndrome, enchondromatosis, hemangiomas, Ollier' s disease, skull base, chondrosarcoma.

Síndrome de Maffucci complicada por condrossarcoma intracraniano: dois novos casos ilustrativos

RESUMO - Síndrome de Maffucci é uma condição congênita rara, às vezes confundida com a doença de Ollier, caracterizada por encondromas múltiplos associados com hemangiomas e flebectasia. A concomitância com neoplasias primárias tem sido relatada esporadicamente. Nós relatamos dois casos de síndrome de Maffucci associada a condrossarcoma da base do crânio, enfatizando aspectos fisiopatológicos e o manejo desafiador dos condrossarcomas intracranianos. Em revisão da literatura, podemos encontrar o relato de apenas doze casos similares.

PALAVRAS-CHAVE: síndrome de Maffucci, encondromatose, hemangiomas, doença de Ollier, base de crânio, condrossarcoma.

In 1881, Maffucci[1] first described a rare condition originally characterized by childhood onset of multiple hemangiomas and multiple enchondromas in subjects with no previous family history. In 1900, Ollier[2] described a similar congenital enchondromatosis without hemangiomas. In reviewing the literature on Maffucci's syndrome, the authors highlight the difficulty involved in making a definitive diagnosis in rare conditions with similar pathology[3].To the best of our knowledge, these two conditions as reported in the literature were thought to be distinct entities, but some authors suggest that both syndromes represent a spectrum of the same disease process rather than two distinct diseases[4,5]. Actually, it has been suggested that all patients diagnosed to have Ollier's disease should be screened with total body magnetic resonance imaging (MRI) to exclude the presence of hemangiomas and other associated occult malignancies[3]. Although the prevalence of malignant changes in skeletal lesions in Maffucci's syndrome and Ollier's disease is quite similar, it is important to differentiate between these two conditions because of the greater risk of developing nonmusculoskeletal malignancies in the former[6,7]. At the present time the exact cause of Maffucci's syndrome is unclear. Some authors believe it is a result of chromosomal abnormalities[8,9]. Others believe it is a congenital mesodermal dysplasia[3,10].

In a review of the literature, we were able to find 209 reports of Maffucci's syndrome[4,5,11-13]. Twenty-sev-

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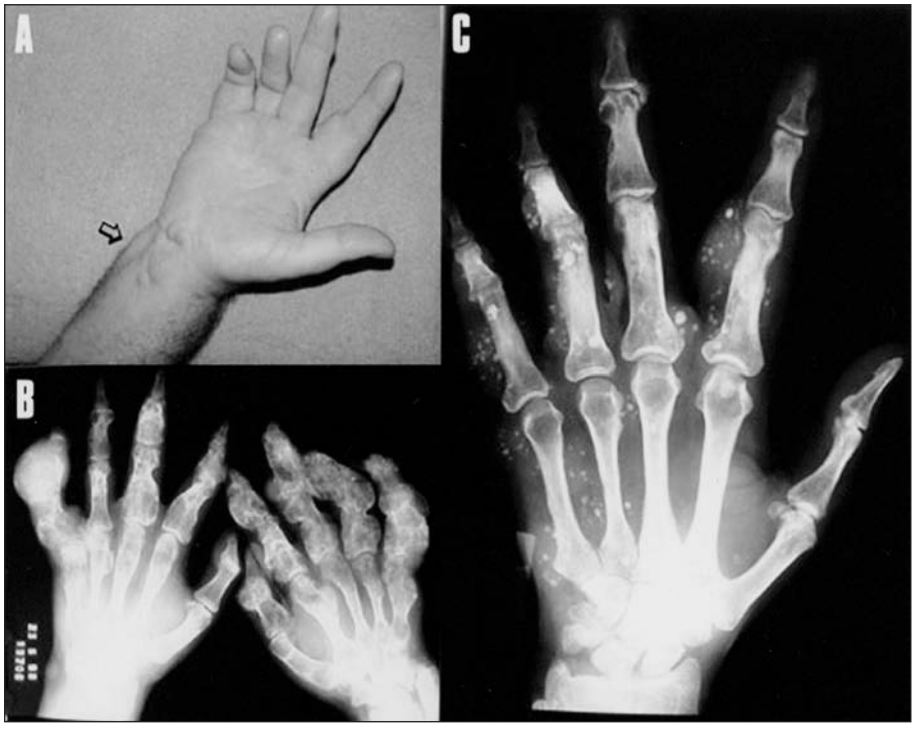

Fig 1. A (Patient 1), the skin of his wrist shows areas of bluish discoloration consistent with hemangiomas and phlebectasia. B (Patient 2), radiograph of the hands shows multiple radiolucent lesions with osseous expansible remodeling. C (Patient 1), radiograph of the hand shows well-defined round calcifications in the soft-tissue masses, typical of phleboliths.

en of the reported patients had intracranial lesion, but only 12 presented with intracranial chondrosarcoma. Two new cases of chondrosarcoma of the base of the skull associated with Maffucci's syndrome are discussed in the light of the literature. It was obtained the patient's informed consent and approval from the Hospital's Ethics Committee before submitting this paper.

CASES

Case 1 – A 42-year-old male patient was referred to our department complaining of headaches and progressive visual disturbance. He also had developed temporal lobe epilepsy which had been treated with anticonvulsive therapy.

He had developed multiple palpable nodular masses on both hands since the age of 18 years. The skin of his wrist showed areas of bluish discoloration consistent with hemangiomas and phlebectasia (Fig 1), which had been present since childhood. Radiographs of the hands showed multiple well-defined, irregularly expanded, radiolucent lesions in the digits of both hands. Radiographs of the right hand also showed multiple phleboliths, typical of cavernous hemangiomas (Fig 1). At initial assessment the diagnosis of Maffucci' s syndrome had been made. Computed tomography (CT) and MRI scans revealed an extensive right-sided skull base tumor affecting the petroclival region and involving the cavernous sinus (Fig 2). A right frontotemporal craniotomy was performed, revealing a gelatinous tumor extending from the clivus to the suprasellar region and impinging on the hypothalamus. The tumor was debulked with suction aspiration once its downward retraction was thought

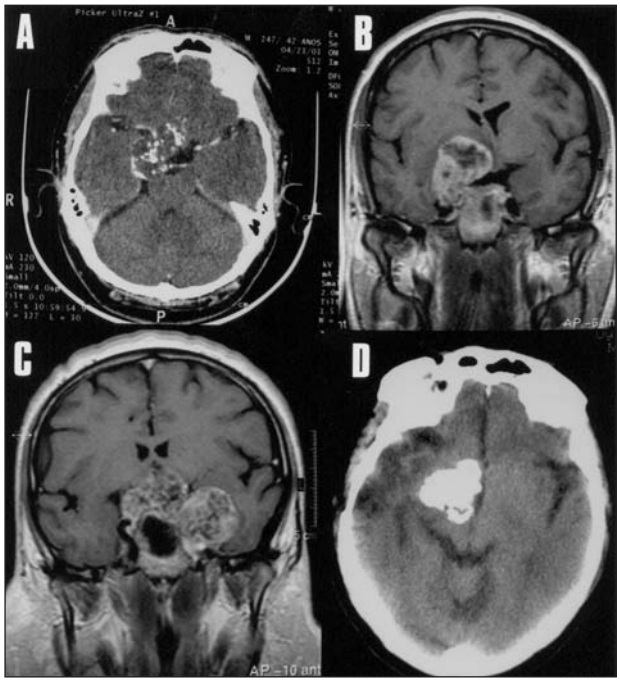

Fig 2. A (Patient 1), axial enhanced CT scan showing a mass in the cranial base extending from the right parasellar region to the clivus. B (Patient 1), coronal T1 weighted gadolinium-enhanced MRI scan revealing the same lesion; it was invading the right cavernous sinus and impinging on the hypothalamus. C (Patient 2), coronal T1 weighted gadolinium-enhanced MRI scan showing a left petroclival, heterogeneously enhancing lesion; it was invading the cavernous sinus. D (Patient 1), axial CT scan after radiotherapy showing calcification of the residual tumor.

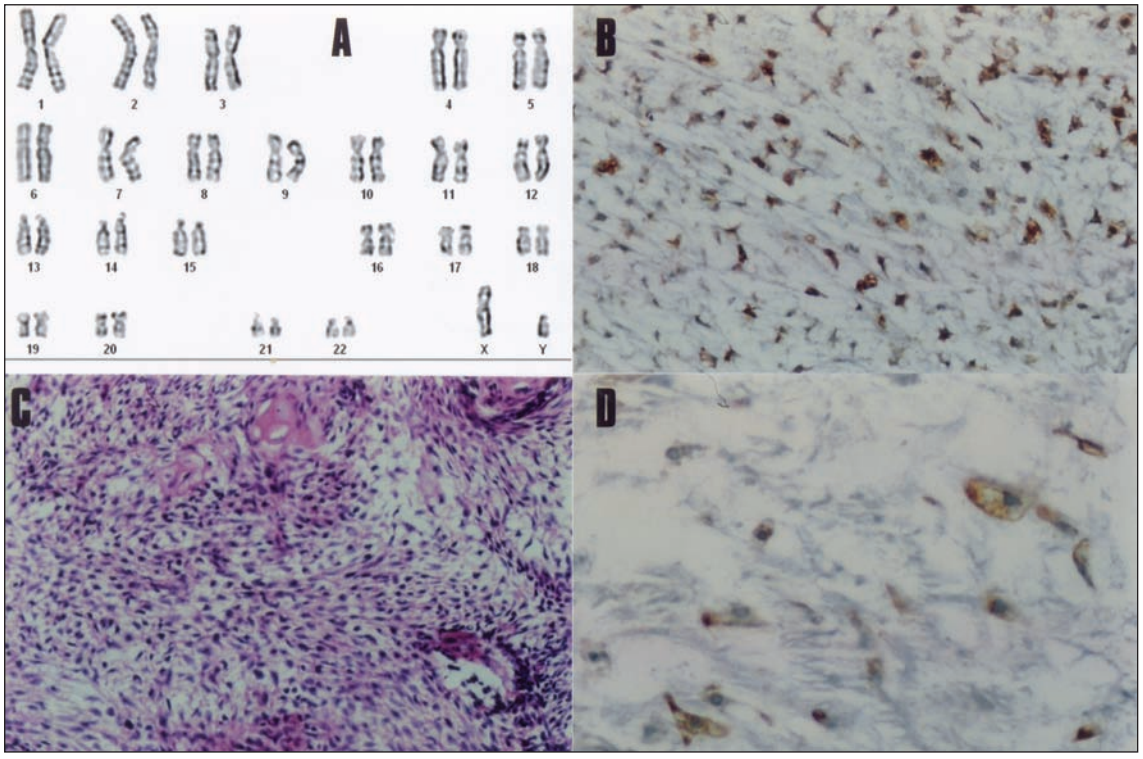

Fig 3. A (Patient 2), normal karyotype. B (Patient 2), positive s100 protein staining. C (Patient 2), photomicrograph (original magnification, x40; hematoxylin-eosin stain) showing atypical cartilaginous proliferation made of lobules of cells with mild nuclear pleomorphism immersed in large areas of chondroid matrix. D (Patient1), positive vimentin staining.

too dangerous. After extensive piecemeal removal, the tumor origin was found to be at the petrous apex of the temporal bone with extensive infiltration and, despite drilling, only partial removal was possible. After the operation, the patient developed right oculomotor nerve palsy.

The histopathological examination showed atypical cartilaginous proliferation made of lobules of cells with mild nuclear pleomorphism immersed in large areas of chondroid matrix. There were some foci of bone invasion by lobules of tumor cells.

Immunohistochemical study showed tumor cells positive for vimentin and S100 protein. The histological diagnosis was chondrosarcoma (Fig 3). The patient underwent radiotherapy for the residual tumor. At follow-up 3 years later, the residual tumor became almost completely calcified (Fig 2) but the patient presented hepatic metastasis and ascitis. In spite of clinical investigation, no other primary malignancy was demonstrated and the patient died due to pulmonary complications.

Case 2 – A 34-year-old man originally noticed multiple hard nodules on his hands fingers when he was 8 years old. He developed subcutaneous soft masses in a progressive pattern. He was known to have multiple enchondromas of the phalanges of both hands (Fig 1) and feet, and long bones of the right forearm and lower limbs. He had undergone a number of orthopedic procedures on his fingers and left tibia. There was no family history of any enchondromatosis and he had been diagnosed as Ollier s disease.

The patient complained of neurological symptoms, such as visual loss, double vision and headaches, two months before admission. The major clinical findings were asymmetrical leg shortening, tumescent lesions on hands and feet and a typical hemangioma on the abdominal skin. The diagnosis was revised to Maffucci s syndrome.

The CT scans showed an intracranial mass arising in and eroding the petrous apex and clivus on the left side. The T1-weighted MRI scans showed a low intensity mass extending from the left side of the clivus to the parasellar region (Fig 2). A left frontotemporal craniotomy was carried out and a tumor compressing the optic cranial nerve was extensively removed. The postoperative course was uneventful, but transitory abducent nerve paresis was observed. The histological diagnosis was chondrosarcoma, which was confirmed by immunohistochemical studies (Fig 3). In this case, chromosomal study was performed but no significant abnormality was found (Fig 3).

At 2-year follow-up, the CT scans showed growing of the tumor. The patient declined any surgical intervention or adjuvant therapy and remains stable, at 11-month follow-up.

DISCUSSION

Maffucci s syndrome is a disorder in which multiple enchondromas of the long bones are associated with hemangiomatosis and phlebectasia[10]. Maffucci s syndrome is a congenital non-hereditary condition

that usually presents before the onset of puberty; there is no family history. In 25% of cases, the clinical symptoms of Maffucci' s syndrome are present at birth or manifest in the first year of life, and in around 80% the symptoms start before puberty[14]. The subjects usually appear normal at birth, the lesions becoming noticeable in childhood because of deformity, fractures, or the appearance of enchondromas or hemangiomas[10]. The major clinical findings are asymmetrical leg shortening, tumescent lesions on the hands and feet and occasionally fractures through the affected areas. The skeletal and vascular lesions in the extremities are usually asymmetrically distributed[8,14]. The disease progresses and gives increasing disability, but may become static after the growth period has ended.

The vascular abnormalities of Maffucci's syndrome consist of multiple cavernous hemangiomas and phlebectasia[10,14]. The capillary or cavernous hemangiomas are most commonly seen on the skin as dark blue patches or nodules arising from the subcutaneous tissues, compressible and sometimes tender on pressure. However, deep hemangiomas occurrence is not uncommon (lips, oropharynx, intra abdominal and gastrointestinal)[8,14,15]. Thrombi may form and sometimes become calcified; as phleboliths they produce a striking radiographic picture in the soft tissues (Fig 1). Phlebectasia is common and may affect large groups of veins or be confined to a few local areas in a vein, causing bead-like swelling (Fig 1).

Maffucci' s syndrome is sometimes confused with Ollier's disease, synonymous with multiple enchondromatosis, which was described 19 years later and consists of multiple enchondromas without hemangiomas[2]. Both are congenital but not hereditary enchondromatosis (a mesodermal dysplasia syndrome). Enchondromas result from failure of normal enchondral ossification beneath the growth plate. There is a derangement of cartilaginous growth, which results in migration of cartilaginous rests from the epiphyseal plate into the metaphyseal regions. Proliferation of these bits of cartilaginous tissue leads to the development of intraosseous chondromas[5].

The multiple enchondromas have a particular site predilection- the long bones of the legs and arms and the phalanges being by far the most commonly affected. Often they can be more extensive involving not only the above sites but also the ribs, vertebrae, and the skull[8]. Since these tumors occur in areas derived from cartilaginous matrix, the intracranial lesions invariably arise at the skull base, that is embryologically derived from cartilage. The sphenoid bone was found to be the most common site of enchondromas of the skull in both Maffucci' s syndrome and Ollier's disease[16,17].

It is well known that Maffucci' s syndrome is associated with an increased risk of malignancy[3]. In Maffucci' s original paper he noticed that these patients developed malignant neoplasms particularly in association with their enchondromatosis[18].

The predisposition to neoplasia is not just confined to the skeleton and these syndromes can be associated with benign or malignant tumors. Schwartz et al.[17] using the life-table method, calculated that 100 per cent of those with Maffucci' s syndrome and 25 per cent of those with Ollier s disease would eventually develop a malignancy.

Vascular sarcomas including angiosarcoma and lymphangiosarcoma have been described along with fibromas, adenomas, ovarian teratomas, gliomas, pituitary adenomas, pancreatic adenocarcinomas, spindle cell haemangioendotheliomas, thyroid adenomas, esthesioneuroblastoma and chordoma. Malignant transformation of nonmesenchymatous and mesenchymatous tumors has been reported more frequently in Maffucci' s syndrome than in Ollier's disease[5,15,19-22].

The largest review of Maffucci' s syndrome was made by Lewis and Ketcham[13] when they studied 105 cases and found the incidence of sarcomatous transformation of the enchondromas to be 15 per cent, and the overall incidence of malignant tumors in this group of 105 patients to be as high as 23 per cent. Some authors have reported an incidence of associated malignancies of 50% or more[4,6]. Among cases of malignancies associated with Maffucci's syndrome, less than 10% were located in the base of the skull and less than half of these tumors were chondrosarcomas[4]. This incidence appears to be lower in Ollier's disease.

Intracranial chondrosarcomas are rare lesions of the base of the skull usually arising from the sphenooccipital and spheno-petrosal synchondroses or from the parasellar region[23]. In general, they are infiltrative, malignant tumors of cartilage-producing cells and represent between 0.15 and 15% of intracranial tumors[24,25]. The symptoms of intracranial chondrosarcomas may not appear for many years since the tumors are slow growing and cranial nerve involvement is usually the most prominent clinical finding. Immunohistochemical studies are necessary to differentiate well-differentiated chondrosarcomas from some chondroid chordomas and from metastatic car-

cinomas[5,12]. Chondrosarcomas are mesenchymal tumors positive for vimetin and S100 protein.

Initially the sarcomatous transformation was thought to be more significant in Maffucci' s syndrome than in Ollier's disease thus making the differentiation between the two conditions more relevant. Mellon et al.[14] described malignant changes in Ollier's disease and suggested that the multiple hemangiomas seen in Maffucci' s syndrome may be subtle or sub-clinical. He then went on to suggest that Maffucci' s syndrome and Ollier s disease were not two separate entities. These descriptions have therefore led some authors to question the distinction between the two syndromes. Ollier's disease and Maffucci's syndrome could represent two entities within a continuum of multiple enchondromatosis[4,17].

In several case reports, we found that at time of the diagnosis of chondrosarcoma, the patient was first considered to present Ollier's disease, but the concomitant diagnosis of a hemangioma indicated a correct diagnosis of Maffucci's syndrome[3-6,14,26-28]. Recently it has been suggested that all patients believed to have Ollier s disease should have total body MRI to search for hemangiomas and other associated malignancies and thus make the correct diagnosis of Maffucci' s syndrome[3].

At the present time the exact cause of Maffucci' s syndrome is unclear. Some authors believe it is a congenital mesodermal dysplasia, since both the hemangiomas and dyschondroplasia are mesodermal in origin[29]. It was emphasized that this syndrome is actually mesodermal dysplasia and, as a result, also includes neuroectodermal dysplastic cases associated with pituitary adenoma or glioma. Nakayama et al.[12] go farther in saying that Maffucci' s syndrome is not only mesodermal dysplasia associated with neuroectodermal dysplasia but may also include neuroectodermal dysplasia with a high relative risk of intracranial neoplasia. It confers upon the individual patient a genetic proclivity for development of one or more brain tumors.

Regarding chromosomal research, Saavedra et al.[27] reported that this syndrome is not associated with any chromosomal abnormality. Matsumoto et al.[9] reported inversion of p11 and q21 of chromosome 1 in a patient with Maffucci's syndrome and Nakayama et al.[12] demonstrated an excess of heterochromatin in the q band of the same chromosome (but this can be a normal polymorphism) in a chordoma associated with Maffucci's syndrome. The relationship between this syndrome and chromosomal abnormalities is still not fully known and cytogenetic studies in Maffucci' s syndrome are limited. We did not find any chromosomal abnormality, but we can not exclude microdeletion or mosaicism. Management of Maffucci's syndrome aims at relief the symptoms and early detection of malignancies. Operative procedures for the skeletal lesions and sclerotherapy, irradiation, and surgery for the vascular lesions have been described[6]. Skeletal or soft tissue lesions that enlarge or become painful without antecedent trauma should raise the suspicion of malignancy and need to undergo biopsy[14].

The treatment of choice for these intracranial cartilaginous tumors is complete surgical excision but this is often difficult to achieve due to difficult access and relationship with neurovascular structures. Cranial nerve palsies are common not only as clinical presentation but also as postoperative complication. In most patients, debulking was the main goal of surgery, and clean margins were not achieved. The benefits of aggressive cytoreduction must be balanced against the morbidity associated with surgery. The gross total resection or a maximum safe cytoreduction surgery can be achieved using cranial base techniques, but a longer follow-up period is necessary to ascertain that radical resection was achieved. Chondrosarcomas tend to be slow growing tumors with a propensity for recurrence, and thus clinical and radiographic follow-up is necessary indefinitely[5].

There is currently no effective chemotherapy for these tumors. As radiation is not a benign treatment and given the slowly progressive natural history of chondrosarcomas, some authors believe that radiation should be reserved for select cases[28]. Patients with symptomatic disease progression have the option to repeat surgery, radiation therapy, or both. Because there is residual tumor and recurrence in the majority of the cases, other authors believe that early radiotherapy treats better these tumors when they are smaller. They favor radiosurgery after partial resection rather than observation, but there is no data to suggest that one approach is better than the other. Proton beam radiotherapy and radiosurgery seem to be effective adjuvant treatments for cranial base chondrosarcomas[30]. Although originally reserved for recurrent symptomatic lesion progression, adjuvant treatment at the time of initial resection has become more prevalent. When remnants are observed on postoperative MRI, the patients should be referred for proton beam radiotherapy or radiosurgery. Rosenberg et al.[24] reported 10-year control rates in the range of 98% with adjuvant radiothera-

py in patients with chordomas and low-grade chondrosarcomas. Crockard et al.[20] and Wanebo et al.[21] reported a 5-year survival rate of 93%. We must consider that these results cannot be simply extrapolated to a patient with Maffucci' s syndrome because of the co-morbidities associated to this syndrome.

In conclusion, we also propose that Ollier's disease and Maffucci' s syndrome are two manifestations along a spectrum of dyschondroplasia, probably a different phenotypic expression of the same genetic disorder. It would probably be more accurate to distinguish Ollier-type and Maffucci-type multiple enchondromatosis as stated by Noel at al.[4]. Both disease variants are associated with a risk of mesodermal and non-mesodermal malignancies, including intracranial chondrosarcomas. In the light of this, appropriate differential diagnosis between these two conditions and screening patients are mandatory. Further analysis employing immunohistological and detailed cytogenetic studies, including searching for microdeletions and mosaicisms are still necessary to elucidate the real nature of this syndrome. The treatment of choice for cranial base chondrosarcomas is total removal of the lesion, but multimodality therapy, which also includes radiation therapy, and radiosurgery, is the ideal overall treatment strategy for the patients with this stigmatizing disorder.

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