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Mafucci syndrome case series of 2 patients and current literature update and advances

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Abstract
Introduction: Maffucci syndrome is a rare congenital chondrogenic disease characterized by multiple cartilaginous tumors (central enchondromas) associated with multiple cutaneous hemangiomas (spindle cell subtype). The patients have a high incidence of malignant transformation and 100% risk of skeletal/extraskeletal malignancy.
Study Design: Case reports of two patients and updated literature review.
Objective: The purpose of this study was to perform an updated review and present our experience with two cases of mafucci syndrome, including ongoing treatment strategies and followup concerns.
Methods: A detailed description of a cases and an updated literature review.
Results: Both patients under review demonstrated classical signs of maffucci: multiple enchondromas with polyostotic dysplasia and quadrimelic hemangiomas. One patient had been on follow-up for 17 years. It was interesting to find both patients had a left limb deformity and hemangioendothelioma predominance. Recent literature proposes proteomic biological analysis and karyotyping for IDH1/2 mutations.
Conclusion: Maffucci syndrome cases are aptly rare and patients need close routine follow-up for early detection of skeletal or non-skeletal malignancies.

Keywords: Spindle cell hemangiomas, enchondroma, multiple enchondromatosis, chondrosarcoma

Introduction

Maffucci syndrome (MS) (Online Mendelian Inheritance in Man number 166000) is a rare disorder characterized by multiple enchondromas closely associated with superficial and deep low grade spindle cell hemangiomas. It is classified within a spectrum of 6 types of enchondromatoses categorised by Spranger, depending on the enchondromas distribution, clinical findings as shown in table 1 below. Halal and Pansuriva [1, 2] have proposed modifications and alternatives to this classification with the former proposing 3 more categories to the Spranger classification. Rarer subtypes of enchondromatosis include metachondromatosis, genochondromatosis, spondyloenchondrodysplasia, dysspondyloenchondromatosis and cheirospondyloenchondromatosis [2].

MS is rare with less than 200 cases documented with an equal male and female preponderance and no racial or ethnic preference. It commonly occurs between ages 4 and 5 years but only 25% of reported cases are congenital. No familial inheritance has been demonstrated [3]. It is characterized by a mosaic pattern somatic mutations in the isocitrate dehydrogenase 1 (IDH1) or IDH2 genes, proposed to be culpable for enchondromas, chondrosarcomas and non-sarcomatous neoplasms (glioma, glioblastoma, acute myeloid leukemia, and intrahepatic cholangiocarcinomas (IHCC)) [4, 5].

Clinical features may be detectable postnatally but do not generally become apparent until ~5 years of age. Patients usually have a normal epidemiological lifespan with unaffected intelligence. Due to the associated bone deformities patients have a short stature and muscular atrophy/ underdevelopment with minimal functional impairment depending on individual skeletal deformities [6, 7]. We present two case reports to document clinical findings and interventions in patients followed up at Pernambuco Cancer Hospital and demonstrate the multidisciplinary care despite diagnostic limitations in our context.

Table 1: Spranger Classification of Enchondromatoses

Type/ class	Name	Classic radiographic finding	Inheritance pattern	Chromosomal location	Gene	References
Type I	Ollier disease (OMIM 166000)	Multiple enchondromas: Flat and tubular bones, vertebrae and skull evenly distributed	AD or sporadic	3p22p21.1	PTHR1	[6, 8, 9]
Type II	Maffucci syndrome (OMIM 166000)	Similar to Ollier disease but with multiple spindle cell hemangiomas	sporadic	–	somatic IDH1 and I DH2	[5, 9, 10]
Type III	Metachondromatosis (OMIM 156250)	Multiple enchondromas with prominent short tubular bones calcifications	AD	12q24.1	PTPN1	[11, 12]
Type IV	Spondyloenchondrody splasia	Asymmetric distribution discrete enchondromas of long tubular bones, generalized severe platyspondyly, minimal or no feet/hand involvement	AR	19p13	TRAP	[13, 14]
Type V	Enchondromatosis with irregular vertebral lesions	Long tubular and flat bone multiple enchondroma, generalized irregular vertebral body dysplasia of vertebral bodies, hand and feet no/rarely involved	sporadic	–		[2, 9]
Type VI	Generalized enchondromatosis	Generalized evenly distributed enchondromas, severe hand and foot involvement, mild platyspondyly, skull deformity	sporadic	12p11p23	dupl PTHLH	[15, 16]

Enchondromatosis (synonymously called dyschondroplasia) is polyostotic hamartomatous metaphyseal chondrocyte proliferation. It causes adjacent cortical thinning and bone growth distortion causing subsequent deformities such as genu valgus, reduced bone length and pathological fractures in severe cases [2, 17]. Intracranial or vertebral enchondromatosis can cause compressive neurological manifestations [16, 18].

Enchondromas are benign tumors due to abhorrent endochondral ossification centers within the diaphysis or the metaphysis of long bones. They are symmetric and can appear anywhere, be unilateral or bilateral and are commonly found incidentally on radiographs. On conventional radiographs, they appear as metaphyseal/diaphyseal multiple osteolytic, oval-shaped lesions with well-defined margins in long tubular and flat bones [2, 17, 19].

The hemangioendotheliomas associated with MS commonly occur in fingers and feet and are blue, noncompressible, subcutaneous or cutaneous nodules, sometimes with Phleboliths [20, 21]. Histopathologically they contain more cellular capillary-venous vessels than venous malformations and contain spindle cells. They are sometimes associated with lymphatic malformations. Unlike venous malformations, MS patients have normal D-dimer levels [20, 22].

MS and enchondromatosis patients, have a nearly 100% risk of developing other malignancies (skeletal or non-skeletal) beyond 40 years [23]. Sarcomatous degeneration of enchondromas may occur; Risk of malignant transformation of enchondroma is 40% but most are low grade chondrosarcomas (grade 1 or 2) and are mainly successfully managed by wide surgical resection. They may develop mesodermal neoplasms: glioma, astrocytoma, fibrosarcoma, leukemias, hemangiosarcoma and ovarian tumors as summarized chronologically in table 2 below. 30% of patients develop, non-mesodermal tumors e.g., adenocarcinoma [17, 24, 25]. This necessitates a prolonged clinical follow-up.

Table 2: Literature chronologically-described cases of maffucci syndrome and documented malignancies

Number of patients reported with Maffucci syndrome	Number of chondrosarcoma transformation / skeletal tumour	Number of non-skeletal tumour	Type of non-skeletal tumour	Follow-up	Year of publication	References
1	1 likely clavicular transformation of enchondroma	0		No	1881	[26]
1	0	0		No	1889	[19]
1	0	3	Pituitary Adenoma, Astrocytoma, juvenile granulosa cell tumor		1973	[25]
7	4 (three of whom had 2 neoplasms: 2 with low grade chondrosarcoma and one with osteosarcoma)	3	Biliary cholangiocarcinoma, Pancreatic carcinoma, astrocytoma	Yes	1987	[27]
1	0	1	Astrocytoma		1987	[28]
1	0	1	Astrocytoma		1990	[29]
1	0	1	Ovarian fibrosarcoma	No	1990	[30]
1	0	1	Astrocytoma		1981	[22]
1	0	0		No	2001	[7]
1	0	1	oral and intestinal hemangioma	No	1999	[31]

17	9/17 (53%)	0		Yes	2011	[3]
1	1	1	Hemangioendothelioma	Yes	2012	[20]
1	1	0		No	2012	[32]
1	0	1	Spindle cell hemangioma	No	2013	[33]
1	1	0		No	2013	[34]
1	0	0		No	2013	[35]
1	0	1	Anaplastic astrocytoma	No	2014	[5]
1	1	0		No	2014	[36]
1	0	0		No	2014	[23]
1	1	0		No	2014	[37]
1	1	0		No	2014	[38]
9	1	1	Acute myeloid leukemia and von Willebrand disease	No	2014	[39]
1	1 (Parasellar chondrosarcoma with diplopia from abducens nerve palsy)	0		No	2015	[40]
1	1	0		No	2015	[41]
1	1	0		No	2015	[18]
1	0	0		No	2015	[4]
1	0	1	Intrahepatic cholangiocarcinoma	No	2016	[24]
1	0	0		No	2020	[10]
1	0	1 (had buccal hemangioma)		No	2020	[21]
1	0	1	Multicentric bilateral breast fibroadenomas	No	2021	[42]
1	0	1	Intrahepatic cholangiocarcinoma	No	2021	[43]
1	0	0		No	2022	[44]

Angelo Maffucci (Italian pathologist) is accedited for describing the first patient with enchondromatosis and skin angiomas in 1881 [26]. Almost a decade later, seemingly unknowingly, Alfred Kast and Fredrich Daniel von Recklinghausen followed suit [19]. Subsequntly the name Maffucci-Kast syndrome was adopted due to this apparent "dual discovery" but the latter name has been largely dropped over time [45]. The name Ollier's disease was adopted when Ollier described a patient with enchondromatosis without vascular malformations in 1889 [6, 8].

Case Reports

Case Report 1

A jovial 14-year-old girl first presented as an outpatient non-urgent clinic referral for consult with generalized long bone dysmorphic features and multiple quadrimelic cutaneous hypervascular masses (multiple superficial and deep hemangiomas) at the Pernumbuco Cancer Hospital, Recife Brazil in early 2021. She was the third born to her 42-year-old phenotypically healthy mother, and 52- year-old father. The history revealed no 1st or 2nd degree family history of similar clinical features or any congenital malformations with other children described as being phenotypically normal in stature with no medical concerns and good psychomotor function. Her perinatal history was unremarkable with follow-up at a regional nearby lower tier hospital and delivered via an uneventful vaginal delivery at term. Her neonatal, infancy and childhood medical history was relatively unremarkable. No environmental toxin or radiation exposure could be demonstrated from her history. She had been to a regional lower-tier hospital previously at 4 years due to an incidentally vaguely noticeable left foot heel small hypervascular papules and a hypoplastic left lower limb with subtle length discrepancy notice by the mother due to limping of the child. She had been reassured with no cause for alarm but no concrete diagnosis was given at the hospital. She had reportedly undergone a unilateral epiphysiodesis stapling at 7 yrs in another hospital. She was of good general state at our first review; with axillary temperature of 36.7 °C weight of 27.9 kg (Weight for Age percentile = 94% (+1.64 SD); height at 142 cm (height for Age percentile = 97.6%), Weight For height percentile = 5.82%).

Clinical examination (Fig. 1) demonstrated gross quadrimelic asymmetry with shorter left upper and lower limb grossly with right cubitus varus. She also had multiple classical blue, noncompressible, cutaneous nodules on the fingers and feet classically demonstrating hemangiomas with a left limb dominance (left hand and foot), bassel haggen-like both forearm deformity with left arm rhizomelia. Bilateral coxa valga with genu valgum deformities with Tibio femoral angle left 20 and right 14 degrees. She had a left lower limb length discrepancy of 6cm managed with a shoe raise prescription. Her cardiovascular investigations including an ECG and an echocardiogram was normal. Based on her clinical and radiological workup findings a diagnosis of maffucci syndrome was proposed (in the absence of confirmatory molecular and karyotyping tests) supported by.

Clinical findings

Multiple classical hemangiomas on feet and hands, bassel haggen-like both forearm deformities with left arm rhizomelia and right elbow cubitus varus.

Paraclinical investigative arguments

Radiographs (Fig. 2) showing multiple oval-shaped osteolytic lesions with well-defined margins in the metaphysis and/or the diaphysis of long tubular and flat bones suggestive of enchondromas. These were on her pelvis (diffuse with marked osteolysis of the left ilium alar),

bilateral proximal femur, right acromion, both clavicles, left humerus with proximal varus deformity with rhizomelia, both forearm bassel haggen-like deformities with radiocarpitellar dislocation and negative ulnar variance with wrist ulbar deviation. X-ray demonstrating phleboliths. Histology (Fig. 3) of one of the hemangiomas demonstrating spindle cell hemangioma. Normal serum D-dimer levels differentiating it from venous malformation disorders e.g. Klippel Trenaunay syndrome.

The diagnostic confirmatory test which requires proteomic molecular biology for IDH1/2 and PTHr1 mutations and karyotyping for the chromosome 6 and long arm of chromosome 12 (particularly q13q15 rearrangements) was limited by the high patient cost implication. Due on her asymptomatic state routine scheduled outpatient clinic visits were subsequently scheduled. She however sustained a post traumatic left mid diaphyseal closed tibia/fibula transverse fracture later that year. This was however managed, after deliberation, conservatively with a brace and strict non weight bearing crutch ambulation instructions. Union was achieved well with no fracture-associated significant residual deformity. Due to the known high risk of developing visceral secondary malignancies she was on scheduled outpatient clinic follow-ups bi-annually.

Her followup had been otherwise unremarkable. She, however, noticed increasing pain and a slight increase in size one of the hemangiomatous masses on the plantar aspect of the left foot when she started full weight bearing after fracture acceptable consolidation. Concern for sarcomatous change was suspected and an incisional biopsy was recommended. The biopsy tissue specimen preserved in 10% buffered formalin demonstrated:

Macroscopically

Segment of brownish skin with its subjacent subcutaneous tissue measuring 0.8 x 0.6 x 0.4 cm, showing a raised, ulcerated, brownish lesion, measuring 0.6 x 0.5 cm, 0.1 cm from the smallest edge. When cut, the lesion was brownish, measuring 0.3 cm deep and 0.1 cm from the base.

Several sections for histological examination demonstrated a vascular lesion which favored the diagnosis of spindle cell hemangioma with a cavernous component predominance. Immunohistostaining was positive for both CD 31 (CLONE: JC/70 A) DBS and KI-67(8%). This confirmed a cavernous hemangioma (Fig. 3).

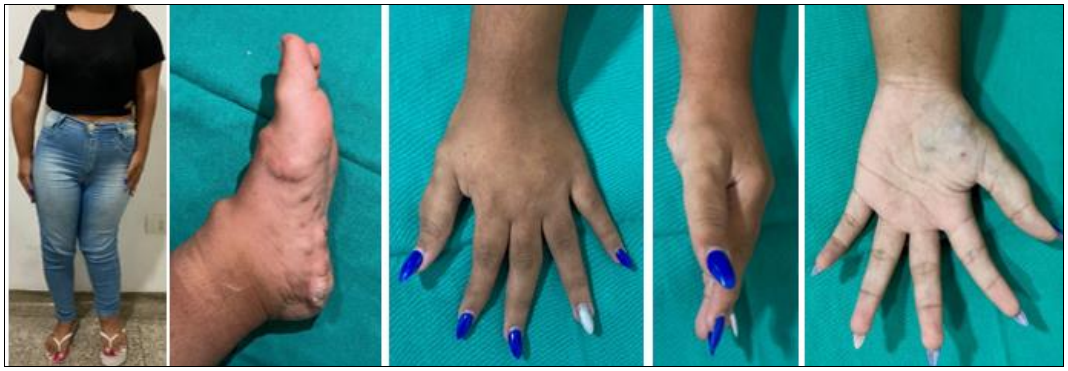
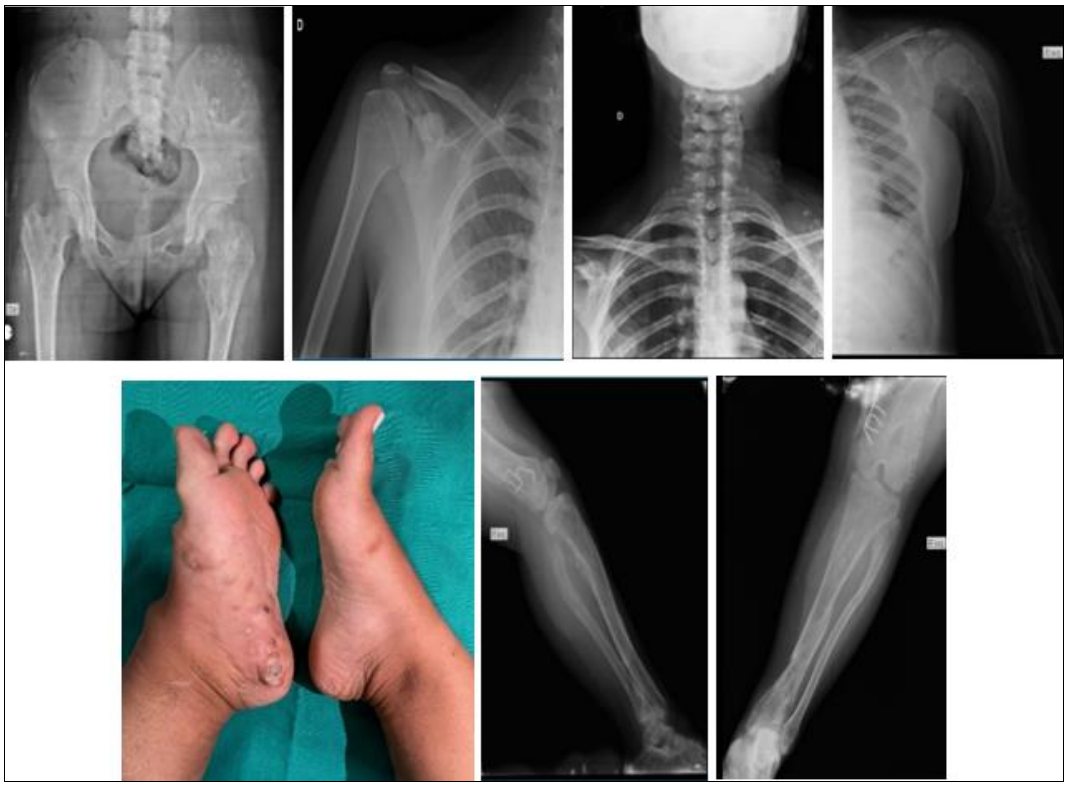


Fig 1: a) Gross clinical findings: quadrimelic assymetry with left arm rhizomelia, right elbow cubitus varus with radial bowing and left knee genu valgus with gross LLD and corrective heel raise sandal. b-f) left foot and hand multiple hemangiomas



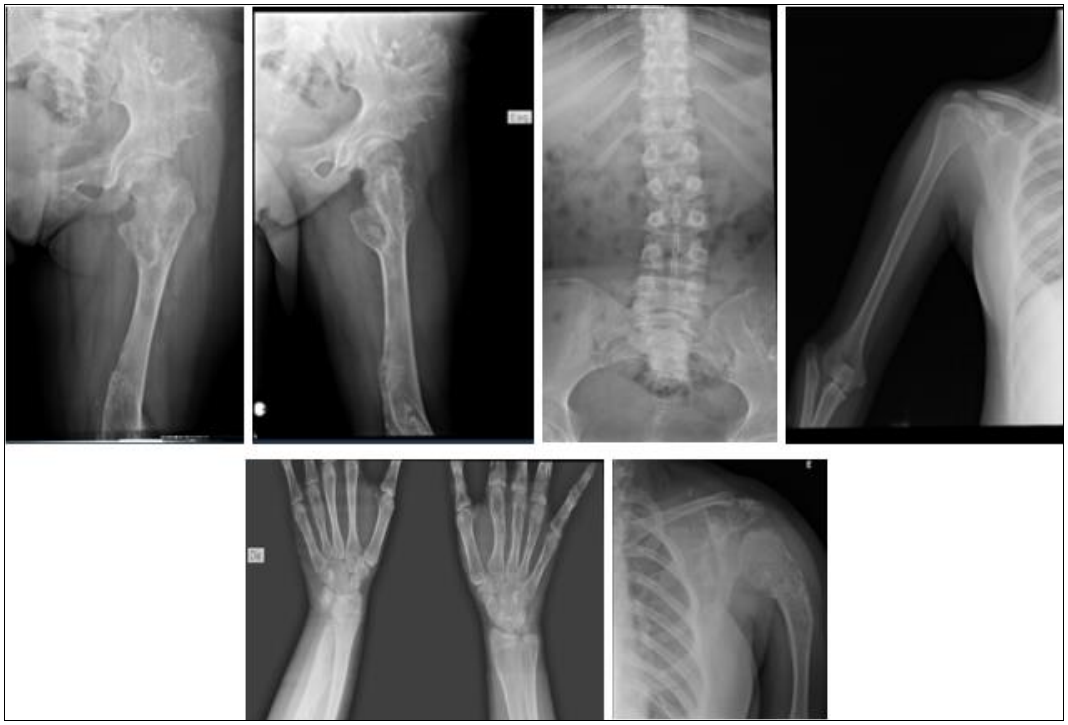


Fig 2: Skeletal survey: polyostotic enchondromas with dysplasia of left proximal humerus (d, l) with shepherd crook-like deformity, lumbar postural left scoliosis (i) and remodelled tibia fracture(e, f) noted epiphysiodesis staples (f)

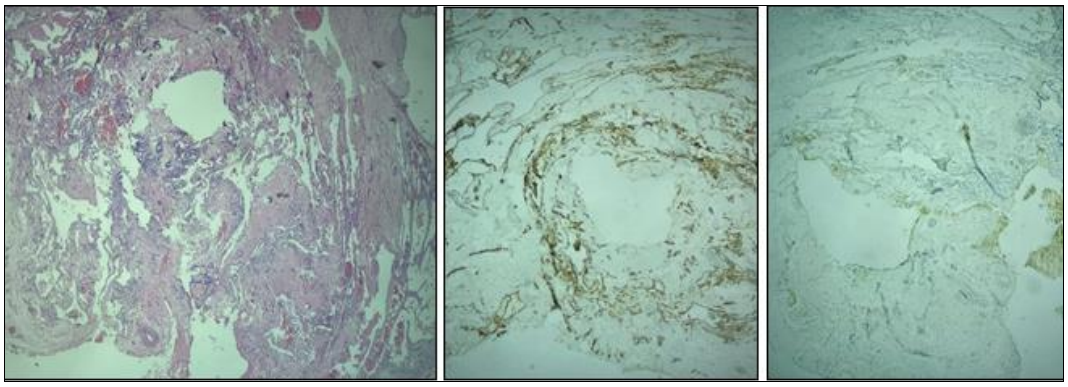


Fig 3: Histology of left plantar hemangioma: spindle cavernous hemangioma. a) Hematoxylin eosin staining; b) Immunohistochemical positive CD 31 (CLONE: JC/70 A); c) Immunohistostaining positivity Ki67.

Case report 2

Another patient, whose follow-up spans 17 years, was a 10-year-old boy at first hospital encounter who first presented as a multiple trimelic cutaneous hemangiomas with local dysmorphic gigantism of the left hand at the Pernambuco Cancer Hospital, Recife Brazil in early 2006. He was the third child to his 18-year-old phenotypically healthy mother, and 25- year-old father at the time of his uneventful term vaginal delivery. His siblings were reportedly of good health with no perceivable similar physical concerns. The 1st or 2nd degree family history was devoid of similar clinical features or any congenital anomalies. Her perinatal history was unremarkable with follow-up at a regional nearby lower tier hospital and delivered via an uneventful vaginal delivery at term. His neonatal, infancy and childhood medical history was relatively unremarkable. No environmental toxin or radiation exposure could be demonstrated from his medical history.

His first hospital review was at estimated at 4 years of age due to bluish hue left hand and foot lesions and a perceived delay in unaided walking by the grandmother at a non-cancer general hospital but no definitive diagnosis or follow-up was initiated. It was only at 10 years (2006) when he was officially referred to the cancer hospital due to the gross left upper limb deformity. His review would then continue uneventfully until 2009 (at 13 yrs of age) when he sustained a traumatic diaphyseal high energy fracture of the left femur that was fixed well with plate osteosynthesis and remodelled anatomically (Fig. 4 and 5). His pre trauma left lower limb genu valgus (Tibiofemoral angle: 18 degrees) and short left limb length discrepancy would persist to stagnate at 7cm at skeletal maturity managed with a shoe raise. He had a rhizomelic left arm with mid forearm deformity. His cardiovascular investigations (ECG and echocardiogram) and laboratory baseline tests were normal.

A diagnosis of maffucci syndrome was proposed (in the absence of confirmatory molecular and karyotyping tests) supported by:

Clinical findings

(Fig. 4 and 5) multiple classical hemangiomas on feet and hands, with the large left local hand gigantism, bassel haggen both forearm deformities with left arm rhizomelia

and cubital valgus, multiple enchondromas with polyostotic dysplastic deformities.

Paraclinical investigative arguments

Radiographs (Fig. 6) showing multiple quadrimelic enchondromas (left > right humerus, with rhizomelic bilateral humerus, bilateral femur, tibia, right acromion, both clavicles, both forearm bassel haggen-like deformity with radiocarpitellar dislocation and negative ulnar variance with bilateral wrist ulnar deviation. Histology (Fig. 7) of one of the hemangiomas (preputial) demonstrating spindle cell hemangioma with epithelial hyperkeratosis. Similarly, karyotyping/ proteomic analysis was not feasible due to cost implications for diagnosis confirmation.

His follow-up had been uneventful and suggested aesthetic left upper limb surgeries had been declined by the patient stating he was functioning optimally with his daily activities. He had even gone ahead to marry and was expecting a newborn by the time of publication of this article. Due to the high risk of visceral secondary malignancies, he is on biannual scheduled follow-ups.

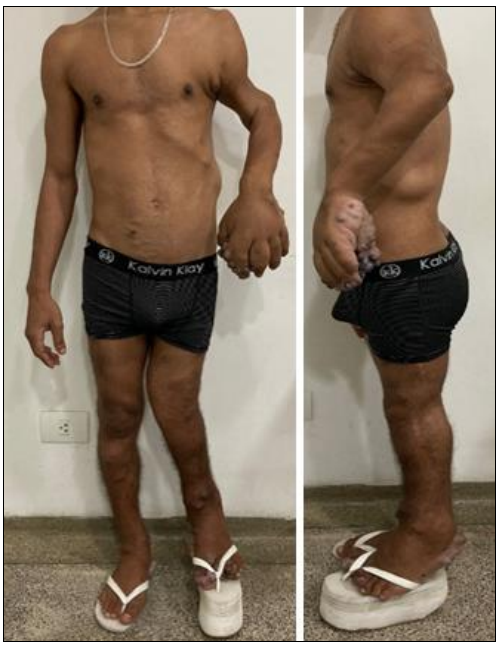


Fig 4: Gross clinical findings: Left hemimelic dysplasia with rhizomelia and hemangiomatous hyperplasia of both left hand and foot

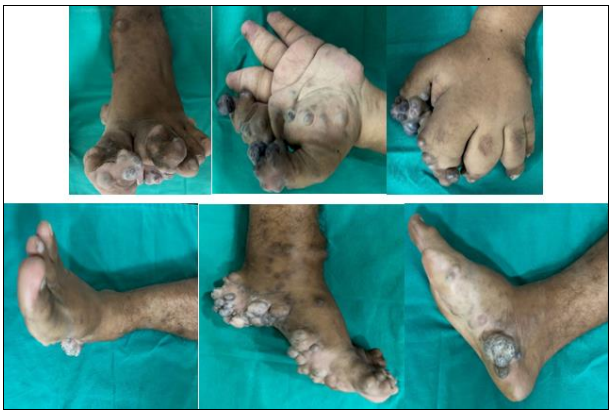


Fig 5: Multiple both feet and hand hemangiomas causing gross hyperplastic dysmorphism

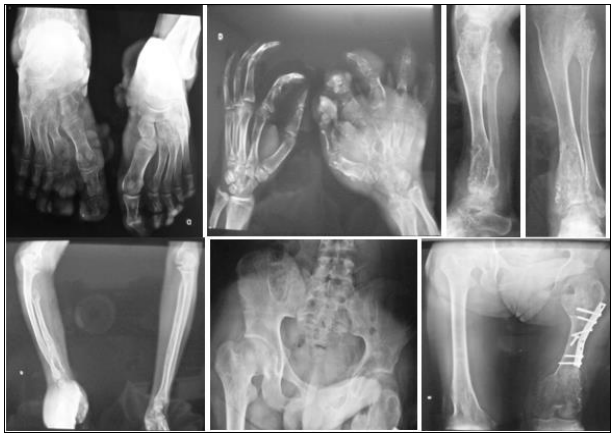


Fig 6: Radiographs demonstrating polysostotic enchondromas, left hand multiple calcified hemangiomas with osteolytic enchondroma lesions(b); left tibia metaphyseal enchondromas with dysplasia(c); both forearm ulnar hypoplasia with radial bowing(d); compensatory standing pelvic tilt(d); remodelled left femur fracture post plate osteosynthesis

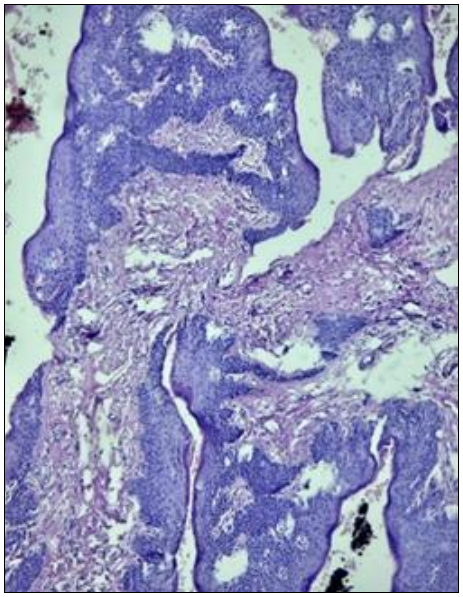


Fig 7: Histology of excised preputial hemangioma showing hyperplastic pseudo-papillomatosis with squamous epithelial keratosis

Discussion

Multiple enchondromatosis syndromes commonly described in literature are Maffucci syndrome and Ollier disease. Olliers has a reported prevalence of around 1 in 100 000 while the reported number of Maffucci syndrome cases in literature is less than 200 [2, 7, 10, 23]. Similarly, to descriptions in literature by, El Abiad *et al*., 2020,these rare conditions are classically nonfamilial as exemplified in both of our patients and are characterized by multiple central (intramedullary) chondrogenic tumours. The former is differentiated from Olliers by its presence of hemangiomas [6]. They both present mostly during childhood. They may also present with gross limb deformities based on the degree of skeletal involvement which is evident in both cases depicted. The intramedullary chondrogenic tumors are metaphyseal and with physiological aging and growth they extend diaphysially in clusters. The molecular similarities of these tumors with normal physis suggests that these tumours are a result of a defect during physiological endochondral ossification [6, 7, 28]. It was however surprising that in both

patients there was a left hemimelic dysmorphic predominance which has not been described in any of the literature perused during preparation of this article.

Malignant transformation and reasons for vascular malformations are unclear but isolated chromosomal abnormalities have been reported in literature. Interstitial deletion, del (1) (p11p31.2) chromosomal defect has been demonstrated in a patient with chondrosarcoma transformation from enchondroma in olliers. Loss of heterozygosity (chromosome bands 13q14 and 9p21) and p53 overexpression have been demonstrated in patients with chondrosarcoma. Presence of mitogenic neurotransmitters in both enchondromas and hemangiomas in a Maffucci syndrome patient, proposes an underlying neural abnormality [4]. If confirmed, it would partially explain predilection of non-sarcomatous malignancies within the central nervous system in Maffucci syndrome [4, 6, 23, 25].

Both have chondrosarcoma transforming potential but it is especially high in Maffucci syndrome, ranging from 17% to 50% of patients [24]. Malignant transformation and development of secondary malignancies such as Gliomas and leukemia (AML) have been attributed to mutations in IDH1 (NM_005896.2) and IDH2 (NM_002168.2). This has been linked to a mutant neomorphic enzyme which catalyzes the reduction of α-ketoglutarate (α-KG) to D-2-hydroxyglutarate (2HG) 5 (oncometabolite). This affects the activity of α-KG–dependent dioxygenases. These subsequently affects a number of cellular reactions, specifically those regulating the epigenetic status of tumuor cells. This is exemplified AML and glioma in which there is global DNA hypermethylation harboring IDH1 and IDH2 mutations. IDH1 /2 genes instruct IDH1/2 enzyme synthesis respectively which catalyse conversion of isocitrate to 2-ketoglutarate. This reaction release NADPH as a byproduct necessary for many cellular reactions/processes [4, 17, 24, 25].

IDH1 or IDH2 mutations, in those causing R132C (c.394C>T; NM_005896.2), R132G (c.394C>G; NM_005896.2, R132H (c.395G>A; NM_005896.2), R132L (c.395G>T; NM_005896.2), R132S (c.394C>A; NM_005896.2) and R172S (c.516G>C; NM_002168.2) amino acid substitutions, have been karyotyped in 56 to70% of periosteal and central chondrogenic tumours. PTH1R (encoding parathyroid hormone receptor 1) mutations have also been reported in patients with Ollier's disease [6]. However, in the resource constrain of our setup it is cumbersome and aptly costly to ascertain the specific karyogenic mutations present in either of our cases. Our cases did not have a clear environmental genetic-transforming exposure as demonstrated in other similar studies in literature. This, however, raises relevant research-based questions that warrant further studies with emphasis on genetic and environmental risk factors.

One of the most important concerns concurring across all literature, for patients with Maffucci syndrome is the necessity for monitoring for malignant transformation and visceral (non-skeletal) malignancies [17, 24]. Initial baseline X-rays of each enchondroma is necessary for future comparison. Technetium 99m-methyl diphosphonate (99mTc MDP) scintigraphy scans have been proposed for chondrosarcoma transformation mornitoring specifically in patients with multiple (>1) enchondromas. For early non-skeletal malignancy detection, abdominal/brain CT scans have been proposed as soon as abdominal or neurological symptoms present but this may be late for some curative interventions [7, 24]. Other authors recommend whole body MRIs annually with concurrent oncological scheduled follow-ups [24].

In this article, we have merely highlighted and questioned some of the traditional views on Maffucci syndrome, specifically regarding the increased malignancy potential and the need for thorough oncological targeted monitoring with lifetime followup. Adjunt to previous described recommendations: acute onset pain should warrant immediate clarification with clinical and radiological examination (plain radiographs, MRI and if needed, CT) is advised.

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Authors' contributions

AM designed and wrote the paper. AMS reviewed the cases and contributed to the design of the paper. EB assisted in consenting with the patients.

Consent

Informed consent to publish the information was granted by both patients.

Competing interests

There are NO competing interests declarable for this article.

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