



## Long term oncologic surveillance in Maffucci syndrome: A case report

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### ARTICLE INFO

#### Article history:

Received 19 June 2017

Accepted 20 August 2017

Available online 26 August 2017

#### Keywords:

Enchondroma

Maffucci

Vascular malformation

Sarcoma

Glioma

### ABSTRACT

Maffucci syndrome is a rare disorder of bone and soft tissue characterized by multiple enchondromas and hemangiomas. Patients with this disorder are at significantly increased risk for malignant transformation of the lesions; of particular note are chondrosarcomas, gliomas, ovarian tumors and other sarcomas. Additionally, patients are affected by skeletal malformations including limb length discrepancies and deformities of the hands, feet and upper and lower limbs. Because of the rarity of the condition, there is currently no consensus for long-term screening of these patients. We suggest a regimen including annual surveillance using advanced imaging and routine physical examination.

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### 1. Background

Maffucci syndrome is a rare disease characterized by enchondromatosis in the presence of vascular lesions.<sup>1</sup> Patients with Maffucci syndrome are at increased risk for skeletal deformity which can cause significant impairment in activities of daily living (ADLs).<sup>2</sup> Patients are also at risk for sarcomatous degeneration of the enchondromas.<sup>3,4</sup> Additionally, there is an association with Maffucci syndrome and multiple soft tissue malignancies, including gliomas,<sup>5</sup> cholangiocarcinomas,<sup>6</sup> ovarian tumors,<sup>7</sup> and other sarcomas.<sup>8</sup>

Here we present the case of a young girl recently diagnosed with Maffucci syndrome and suggest a method of ongoing surveillance for the early detection of malignant transformations of both bone and soft tissue.

### 2. Case presentation

Patient is a 5 year old female who presented with bothersome vascular lesions that are slowly enlarging on her trunk and recently noted in her mouth. She had been seen by Orthopedics for a deformity of her right index finger (Fig. 1).

X-rays demonstrated multiple enchondromas in the hand, pelvis and lower extremities with a marked right sided predominance (Figs. 2–3).

Additionally, she was noted to have a leg length discrepancy of 3.4 cm (Fig. 4).

Based on those findings, she was diagnosed with Ollier's disease. The vascular lesion on her right upper back has been causing her discomfort and becomes irritated when changing clothing. Parents have reported small bluish lesions on the bottom of the right foot and toes as well as subcutaneous nodules along the lateral aspects of the hands, feet and digits.

On physical examination, the patient had normal vital signs for her age (BP 111/67, P 90) and her height was 110.9 cm and weight 19 kg with a BMI of 15.45 kg/m<sup>2</sup>. A complete skin examination was performed and palpation of the skin and subcutaneous tissues of the head, face, neck, chest, abdomen, back and all four extremities. Of note was an 8mm violaceous-erythematous scaly papule localized to the right upper back (Fig. 5).

There was a similar 2 mm red papule on the mid chest. The right lower buccal mucosa demonstrated a plaque comprised of several violaceous papules. There were several firm subcutaneous papules along the lateral aspects of hands, feet and digits including the left hand, the webspace of the right toe and on the right and left foot which also had a faint violaceous hue (Fig. 6). Also noted was a shortening of the right second toe and the aforementioned deformity of the right index finger.

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Peer review under responsibility of Turkish Society of Medical Oncology.



Fig. 1. Right hand with deformity on index finger.



Fig. 2. Enchondromas in finger.

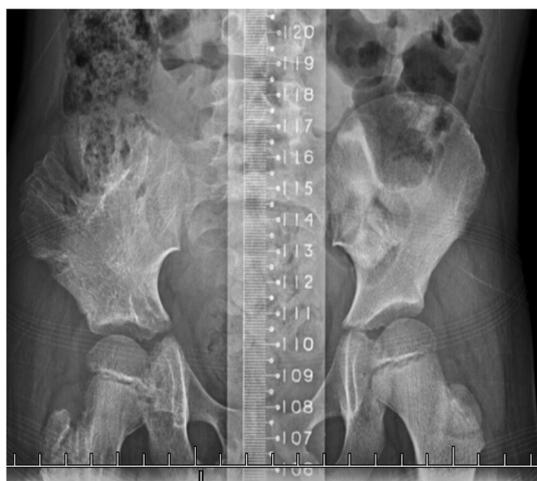


Fig. 3. Enchondromatosis in hemipelvis.

### 3. Treatment

Because of the multiple vascular lesions in the presence of enchondromatosis, the patient was diagnosed with Maffucci syndrome. As she incidentally had already been scheduled for a dental procedure under anesthesia and because the vascular lesion on her back was bothersome, excision of the lesion on the back was performed by plastic surgery and the tissue was sent for pathology.

### 4. Histopathologic findings

Representative areas from the right lesions on the mid chest and

the right upper back were sampled, and 5- $\mu$ m sections from the formalin-fixed tissue were used for routine light microscopic analysis, as well as immunohistological analysis. The antibodies used for immunohistology were CD31 and Glut-1.

The mid chest vascular lesion had dimensions of  $0.4 \times 0.3 \times 0.2$  cm. Unfortunately there was insufficient tissue to be classified. The right back vascular lesion had dimensions of  $0.6 \times 0.5 \times 0.5$  cm in size. Histologic analysis demonstrated appearance typical of a vascular malformation (Fig. 7). Immunohistochemical staining of showed diffuse positive staining for CD31 but negative for Glut-1 also consistent with venous malformation.

DNA was extracted from the areas of viable disease involved tissue for sequence analysis. A single-nucleotide alteration, *IDH1* p.R132C, was identified at low variant allelic frequency. *IDH1* encodes isocitrate dehydrogenase type 1 and somatic mutation of the gene has been associated with vascular and skeletal malformations.<sup>9</sup> Mutations in *IDH1/IDH2* impair the substrate affinity of the enzyme and dominantly inhibit wildtype *IDH1* activity through the formation of catalytically inactive heterodimers.<sup>10</sup>

In recent studies, the *IDH1* p.R132C somatic variant was frequently detected in affected tissue lesions from patients with Maffucci syndrome.<sup>9</sup> In cartilage and vascular tumors, *IDH* mutations are associated with elevated levels of D-2 hydroxyglutarate (2HG) and global DNA hypermethylation.<sup>9</sup> Additionally the p.R132C alteration is a mutational hotspot and has been well described in hematologic malignancies and central nervous system tumors, especially gliomas.<sup>11</sup>

Over 80% of patients with Maffucci syndrome carry somatic mutations in *IDH1/IDH2*.<sup>9</sup>

### 5. Radiologic findings

After the initial radiographs (Figs. 2–4), the patient underwent a full body MRI, which confirmed the presence of multiple expansile T2 hyperintense lesions throughout the skeleton with a right-sided predominance. Additionally, the MRI showed a previously unknown expansile T2 hyperintense lesion in the right sphenoid body (Fig. 8) and multiple expansile T2 hypointense lesions within the spleen.

Follow-up ultrasound of the spleen showed four lesions ranging from  $1.1 \times 1.1 \times 1.2$  cm for the smallest and  $2.3 \times 2.0 \times 1.9$  for the largest (Fig. 9). The lesions were hyperechoic and thought to be consistent with vascular malformations.

Dedicated contrast and non-contrast MRI of the brain showed no evidence of malignancies. There was an expansile heterogenous, predominantly T2 hyperintense enhancing lesion involving the body of the sphenoid and extending into the suprasellar region. The lesion is causing displacement of the cavernous internal carotid arteries, right greater than left with effacement of the right cavernous sinus. There is mild compression of the right internal carotid artery but flow void remains patent. The lesion also displacing the optic chiasm with mild compression (Fig. 10).

### 6. Follow-up

The laboratory evaluation including CBC, CMP, magnesium, phosphorus, creatinine, PT, APTT, IGF-1, growth hormone, TSH, Free T4, cortisol, prolactin, FSH, and LH were all within normal limits for age. Her leg length discrepancy has remained stable and she recently underwent a hemiepiphyodesis of the distal right femur to correct a worsening valgus deformity. She continues to have slow proliferation of the multiple subcutaneous hemangiomas but has not had any recurrence of large hemangiomas.



Fig. 4. Leg length discrepancy.



Fig. 5. Large hemangioma on back.



Fig. 6. Subcutaneous papules.

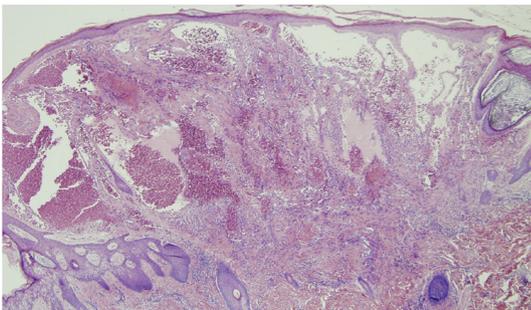


Fig. 7. Microscopic section of back lesion.

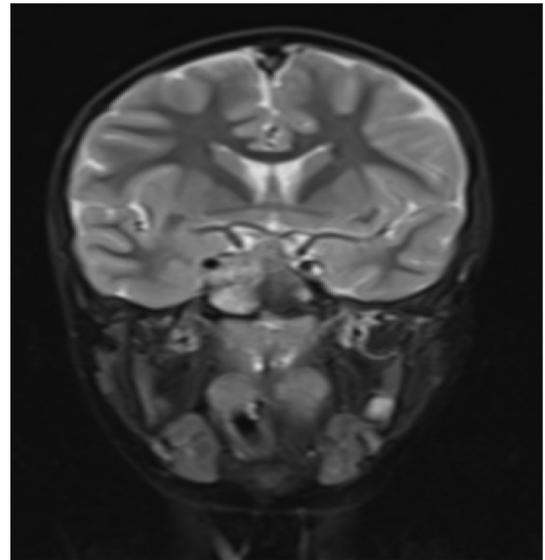


Fig. 8. Brain MRI with sphenoid lesion.

## 7. Discussion

Maffucci syndrome is one of several subtypes of enchondromatosis. Others include Ollier disease, which occurs with more frequency than Maffucci as well as metachondromatosis, genochondromatosis, spondyloenchondrodysplasia, dyspondyloenchondromatosis and cheirospondyloenchondromatosis<sup>12</sup> which are even more rare. While both Ollier disease and Maffucci syndrome are characterized by multiple, often unilateral enchondromas, Maffucci syndrome is distinguished from Ollier disease by the presence of hemangiomas and/or lymphangiomas.<sup>12</sup>

The most common sites for enchondroma formation are the metacarpal bones and phalanges of the hands, however the femur, humerus, tibia and metatarsals and phalanges of the feet can also be affected.

Due to the rarity of the disease the incidence of malignant transformation of the lesions is not known but some reports have estimated it to be between 23 and 100%.<sup>13</sup> Additionally, patients are at increased risk for soft tissue malignancies most notably in the

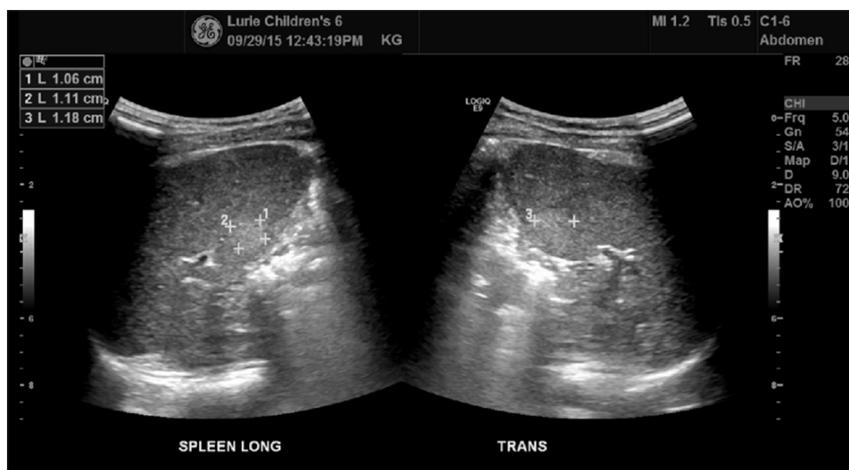


Fig. 9. Ultrasound of spleen with vascular malformations.

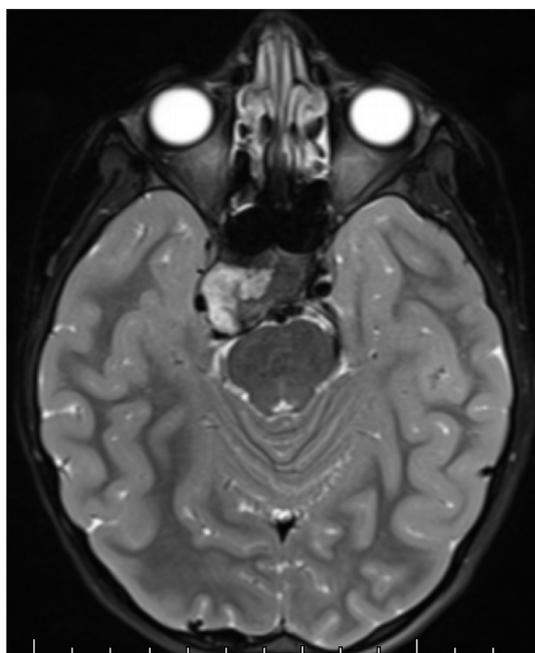


Fig. 10. Brain MRI showing extent of sphenoid lesion.

pancreas, ovaries and brain.<sup>3,5</sup>

There are two primary challenges in the management of patients with Maffucci syndrome. The first is the management of the bony deformities which characterize the disease. Because the unilateral predominance of the enchondromas, there can be significant variation between the hemispheres that can manifest as leg length discrepancies, varus or valgus deformity of the knee and ankle, increased risk for pathologic fracture through the enchondromas as well as malformations in the hands and upper extremities that can interfere with fine motor activities. These challenges are generally managed surgically as they arise and for the lower limbs can include epiphiodesis, limb lengthening surgery using an external fixator (Ilizarov device)<sup>14</sup> or, more recently, a mechanically driven internal fixator device.<sup>15</sup>

The second challenge is surveillance for malignancies, not only the malignant transformation of the primary enchondromas but

also the associated soft tissue malignancies. At present, there is no standard protocol for monitoring patients with Maffucci syndrome. Because of the insidious nature of several of the associated soft tissue malignancies such as ovarian and pancreatic cancer, which are often exceedingly difficult to detect before local or widespread metastasis, we have recommended that this patient undergo annual full body MRI. The advantage of using MRI for this type of screening is not only its ability to detect soft tissue changes but also to monitor the size of the known enchondromas while avoiding multiple exposures to ionizing radiation over the course of a lifetime. Additionally, because of the association with central nervous system tumors, particularly gliomas, we also include a dedicated brain MRI. In this particular patient, the presence of the large sphenoid encephaloma can also be monitored. We are also having the patient in for an annual dilated ophthalmological examination done six months after the annual MRI. Semi-annual physical examination and clinical monitoring by both the clinician and the patient and her family for symptoms suggestive of early malignancies may also be a means for earlier detection and intervention.

## 8. Conclusion

Maffucci syndrome is a very rare disease characterized by multiple enchondromas in the presence of additional vascular lesions. There is a significant increased risk for both sarcomatous degeneration of the enchondromas as well as pancreatic, breast and CNS malignancies.<sup>16</sup> There may be an association with IDH-1 and/or IDH-2 gene mutations and research is ongoing. There is a need for both treatment of the immediate orthopedic aspects of the disease as well as systematic approach to ongoing surveillance for associated malignancies.

## Conflicts of interest

The author declares no conflicts of interest.

## Acknowledgement

The author acknowledges the support of the CAPT James A. Lovell Federal Health Care Center and the United States Department of Veterans Affairs.

The views expressed in this article are those of the author and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

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