

CASE REPORT

Chondrosarcoma of the Hand in Ollier's Disease: Case Report and Novel Approach for Surgical Treatment

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ABSTRACT

Enchondromas are frequent benign cartilaginous tumors that commonly arise in the hand. Ollier's disease is defined by the presence of multiple enchondromas. Malignant transformation of an enchondroma is very rare in the hand. We present the case of a 19 years old girl affected by Ollier's disease, with a rapidly growing enchondroma involving the middle finger with severe bone destruction and soft tissues infiltration. MRI of the hand demonstrated the presence of low signals in T1-weighted sequences and finely uneven medium-high intensity signal in T2-weighted sequences. Histology demonstrated a grade 1 chondrosarcoma, which was treated by a successful conservative surgical approach, with a strict follow-up due to the risk of possible recurrences.

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Key words: Chondrosarcoma; Hand cancer; Ollier's disease

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INTRODUCTION

Ollier's disease, also called multiple enchondromatosis, is a non-hereditary rare syndrome characterized by the presence of multiple enchondromas. Ollier described the disease in 1898^[1], and, afterwards, several reports detailed the clinical and pathological features. Although a common mutation of isocitrate dehydrogenase 1 (IDH1) has been reported^[3], to date, it is not completely clarified whether this syndrome is due to a single mutation in this gene or if it is caused by a combination of mutations (somatic and/or germ-line) involving several genes^[2].

Enchondromas are benign cartilage tumors characteristically arising in metaphysis, diaphysis, and, less frequently, epiphysis of long bones^[4]. Epiphyseal enchondromas severely alter bone growth, deforming shape and length^[4]. Patients usually present asymmetric distribution and extreme variability in terms of size, number, evolution, and localization of enchondromas^[2]. However, in most cases enchondromas are predominantly unilateral and benign^[4].

The prevalence of Ollier's syndrome is estimated to be approximately 1/100000, the peak incidence is in the first decade of life, and the most frequent location is at the extremities^[2]. Two clinical subtypes of the disease are described: enchondromatosis affecting mostly males, transmitted in a Mendelian fashion, and Ollier disease affecting mostly females, with a unilateral growth pattern and without familiarity.

Enchondromas are associated with a number of complications, such as spontaneous fractures, deformities, bone growth deficit, compression of vascular or nervous structures, and malignant transformation to chondrosarcoma (CS).

Although the hand, particularly metacarpals and phalanges, is one of the most common site for the enchondroma development, malignant transformation is extremely rare and, so far, only 12 cases have been reported^[4-9].

In this report we present the case of a 19 years old female affected by Ollier's disease complicated by development of hand CS, with the genetic assessment of the lesion and review of the literature.

CASE REPORT

A 19 years old Caucasian girl affected by Ollier's disease referred to our department for an important dysmetria between the two femurs, and for the rapid growth in the last month of an enchondroma (5×3 cm) involving the first phalange of the third finger (Figure 1 A: Preoperative presentation of the patient's right hand. Note the biggest mass at the third ray and the multiple enchondromas involving the second and the fifth finger; B: Intraoperative image of the neoplasm involving the third ray of the right hand.).

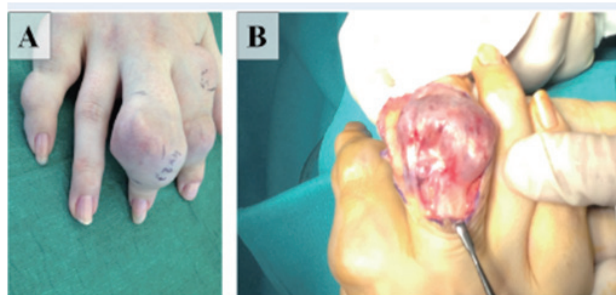


Figure 1 Preoperative and intraoperative presentation of the patient's right hand.

The mass was firm and the skin above the lesion was thin, stretched, and ulcerated at the volar side, with no vascular or nervous deficit. In the previous days, the patient reported severe pain and a yellowish fluid leakage from the ulceration.

Standard radiographs demonstrated severe bone destruction and infiltration of soft tissue. In particular, the lesion showed a thinning of the upper cortex that exceeded the 2/3 of the total cortical thickness, with focal complete cortical breaks. However, only moderate periosteal reaction was seen. The persistence of calcifications gave evidence of a typical form of CS (the major axis of the mass was 5.7 cm).

MRI detected the presence of multiple foci with low signal in T1-weighted sequences and finely uneven medium-high intensity signal in T2-weighted sequences, with deformations of the proximal and intermediate phalanges of the second and the third finger, the proximal phalanx of the fifth finger, the first metacarpal and the distal portion of the second and the fifth finger. These structures were deformed by the expansive lesions, characterized by an intrinsic-extrinsic growth pattern and homogeneous MR signal. The largest mass was located at the volar side of the first phalanx of the third finger, with oval morphology and diameters of 5.2×4.2×3.4 cm, displacing the radial side of the flexor tendon of the middle finger (Figure 2 A and B: Oblique and Frontal XR of the right hand at presentation: note wide tissue component and corresponding cortical interruption of the main lesion at the third finger. C: coronal SE T2w sequences of the main lesion protruding at the ulnar side of proximal and middle phalanges of the third finger D: axial TSE T1w sequence of the main lesion.).

A total body ⁹⁹Tc scintigraphy demonstrated increased uptake in the third, the fourth, and the fifth finger of the right hand, various ribs, the right sacro-iliac synchondrosis, the whole right femur, the proximal part of the right tibia and the second and third fingers of the left foot.

Incisional biopsy specimens appeared pearly white and, at light microscopy, the lesion showed a nodular growth pattern with vascular and stromal internodular septa, with bone erosion and discontinuity of the cortical bone due to focal resorption. Tumor cells were irregularly thickened and characterized by small central hyperchromatic nuclei, clear cytoplasm with ill-defined margins, and separated by abundant fundamental substance, with the final

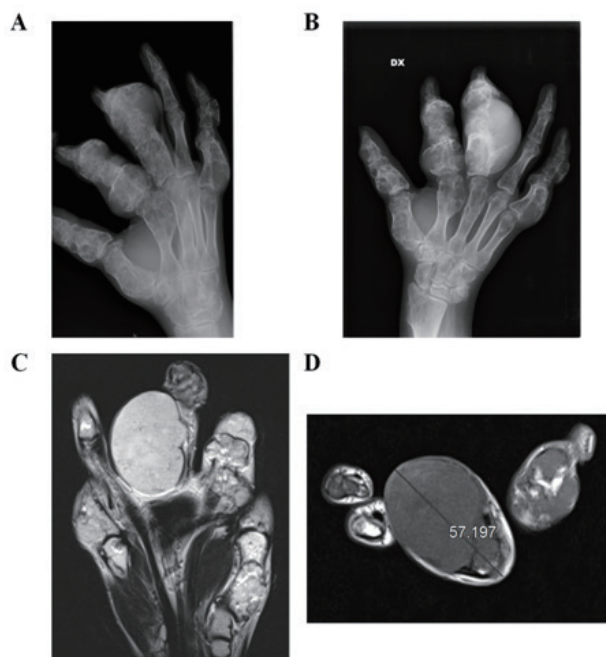


Figure 2 Standard X-ray and MR preoperative study of the right hand.

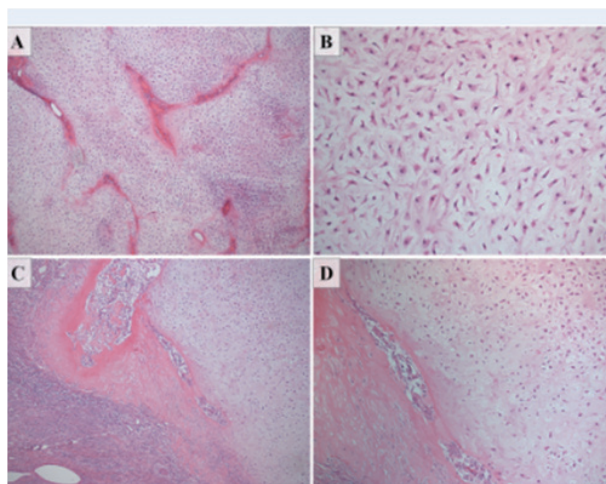


Figure 3 Histological examination of the tumor.

diagnosis of low grade CS in multiple enchondromatosis Total body CT did not reveal parenchymal or lymphatic metastases (Figure 3 A: The tumor showed a nodular growth pattern with vascular and stromal internodular septa. B: Tumor cells were irregularly thickened and characterized by small central hyperchromatic nuclei, clear cytoplasm with ill-defined margins, and separated by abundant fundamental substance. Mitotic index was low (2×10 HPF) C and D: Strong tendency to bone erosion and discontinuity of the cortical bone due to focal resorption were also present. Hematoxylin and eosin stain. Original magnifications 40×,100×, and 200×.).

The young age of the patient, the absence of metastases, and the favorable anatomical position, addressed the surgical choice to an in toto margin-free surgery of the tumor, with reconstruction of the extensor tendon of the third finger. After removal, tumor-free margins were histologically confirmed. No bone autograph was need for the reconstruction of the third finger (Figure 4 A: Postoperative presentation of the patient's right hand B and C: Oblique and Frontal XR of the right hand after surgical excision. Note the wide thinning and destruction of the cortex. D: Coronal SE T1 w IR: after surgery; note the complete removal of the cartilaginous mass

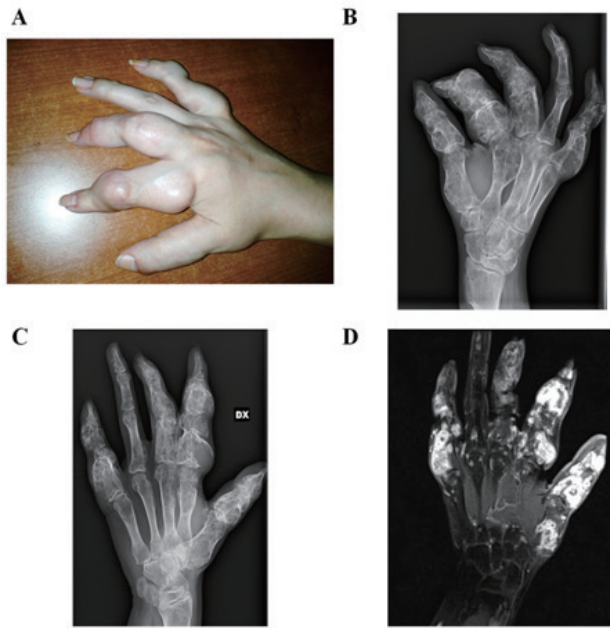


Figure 4 Standard X-ray and MR postoperative study of the right hand.

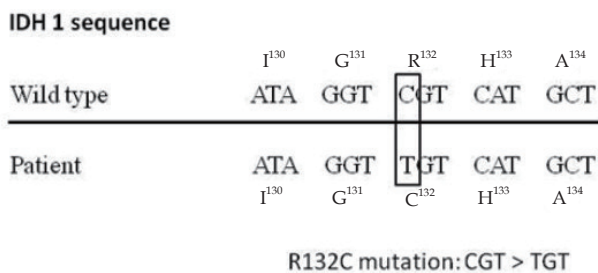


Figure 5 IDH1 sequencing analysis.

on the ulnar side of middle and proximal phalanges of the third finger).

During surgery we also carried out a lengthening of the right femur, with excellent aesthetic and functional results. No radiotherapy or chemotherapy were administered after surgery.

We screened this patient by polymerase chain reaction (PCR) on genomic DNA extracted from the formalin-fixed paraffin-embedded specimen of CS. The sequencing analysis of IDH1 revealed a R132C mutation (CGT > TGT, codon 132) (Figure 5 IDH1 sequencing analysis of CS revealed a mutation involving codon 132.).

DISCUSSION

Ollier's disease is a very rare syndrome: its prevalence is estimated to be 1:100000^[2], being 10 times less frequent than a solitary

enchondroma. This syndrome is defined by the presence of multiple unilateral enchondromas. As the most frequent benign intraosseous cartilaginous tumors, enchondromas develop from normal cartilage and enlarge during normal bone growth. Clinical complications associated with multiple enchondromatosis are bone deformities, dysmetria caused by epiphyses involvement, and malignant transformation.

Malignant CS occurs in about 25% of the patients affected by Ollier's disease by the age of 40 years. As reported in literature, while distal femur, proximal tibia, fibula, and pelvis are common sites of malignant transformation, hand CS in multiple enchondromatosis are anecdotal. Indeed, among the 121 cases of CS reported in the Mayo Clinic survey, no one involved the hand^[4]. So far, only 12 cases of hand malignant involvement in Ollier's disease have been reported, mostly classified as low-grade CS (5-7) (Table 1 Previously reported cases of chondrosarcoma of the hand secondary to Ollier disease.).

Differential diagnosis between "active" chondroma and grade I CS is not possible with histology alone, although hypercellularity, myxoid change, soft tissue infiltration, necrosis, trabecular disruption, permeation, and double-nucleated cells suggest malignant transformation.

The diagnosis of low-grade CS can be established only by integrating clinical, radiographical, and histological features. Classical signs and symptoms of malignant transformation are acute pain, rapid size enlargement, ill-defined margins, cortical bone erosion, bone resorption, and soft tissues invasion. Indeed, as reported by Ryzewicz and colleagues, the main radiological characteristics of chondrosarcoma are the combination of major bone destruction, presence of intralesional calcification, and a periosteal reaction. However, the most suggestive radiographic finding for a high grade lesion is precisely the destruction of the cortical bone. More frequently, especially in tumors characterized by a low degree of malignancy, the cortex does not present a full-thickness lesion but is irregularly thinned and only focally interrupted^[10].

Endo-osteum scalloping is considered a phenomenon due to the host's effort to contain the tumor. Endo-osteum scalloping radiographically involving more than two-thirds of the total cortical thickness with a length that is not less than two-thirds of the tumor, has been reported by Murphey *et al*^[11] to occur up to 75% of chondrosarcomas, but in less than 10% of enchondromas. Another important sign of malignancy is the periosteal reaction. Even this is an attempt by the body to limit tumor progression outside of the medullary canal.

As regards calcifications, Murphey *et al* found that there is a relationship between the density of calcifications and the degree of malignancy of a CS. In fact, the lower-grade lesions tend to be more densely calcified on radiographs compared to high-grade lesions^[11], which have a greater degree of anaplasia and less capacity of calcium deposition.

Table 1 Previously reported cases of chondrosarcoma of the hand secondary to Ollier DISEASE.

Author	Year	Sex	Age	Location	Size (cm)	Grade	Treatment	Follow-up	Recurrence
Current case	2013	F	19	Middle	5	I	Excision	18 mo	No
Muramatsu <i>et al</i> ^[3]	2010	M	78	Little, Ring	10	I	Ray amputation	12 mo	No
Casal <i>et al</i> ^[11]	2010	F	48	Middle, Ring		Unknown	Ray amputation	12 mo	No
Altay <i>et al</i> ^[12]	2007	M	24	Unknown	5	Unknown	Ray amputation	22mo	No
Martinez <i>et al</i> ^[13]	2004	F	53	Little, Ring	5	Unknown	Ray amputation	12 mo	No
Goto <i>et al</i> ^[1]	2003	M	76	Ring	5	I	Amputation	12 mo	No
Goto <i>et al</i> ^[1]	2003	M	27	Little	6	II	Ray amputation	6mo	No
Palmieri ^[10]	1984	M	73	Thumb	3	Unknown	Excision	8 y	No
Palmieri ^[10]	1984	F	81	Index	2	Unknown	Ray amputation	24 mo	No
Palmieri ^[10]	1984	M	62	Ring	3	Unknown	Ray amputation	4 y	Yes
Palmieri ^[10]	1984	M	59	Index	3	Unknown	Ray amputation	3 y	No
Block ^[9]	1977	M	25	Unwnown	7	Low	Ray amputation	7 mo	No

The last critical parameter that directs us to the diagnosis of malignancy is tumor size. Geirnaerdt and colleagues stated that a major axis of greater than 5 cm was the best predictor of malignancy in tumors involving the axial skeleton. The same judgment has been validated also for tumors of the cartilage of the foot. In the current case the cut-off was different. Indeed, at this level the mean diameter of enchondromas was 2.7 cm, while for chondrosarcoma was 5.1 cm^[12].

The gold-standard in CS treatment is represented by surgery, due to radiotherapy and chemotherapy failure. Exner et al stated that phalanx CS are locally aggressive, but compared to CS of other sites, they almost never metastasize^[13]. Based on the excellent survival data reported from 35 cases, Bovee and colleagues assessed that curettage followed by adequate follow-up is a valid approach when technically feasible, although recurrence risk can not be excluded^[14]. Such technique is recommended in those cases in which amputation would cause important disability. Also Dhalin and Salvador declared that curettage, if adequately executed with tumor-free margins, should be considered as curative, even if rarely associated with recurrence^[15].

Contrary to the previous cases reported in table 1, we did not perform a ray amputation. The decision was taken in order to reach an appropriate tumor-free margin debulking of the neoplasm considering the relative young age of the patient.

The patient harbored a mutation of IDH1, which was reported to impair the conversion of isocitrate to α -ketoglutarate (α -KG)^[15]. Such mutation has been demonstrated to affect cellular pathways controlling the epigenetic status of tumor cells in glioma and acute myeloid leukemia. In particular, the R132 mutation of IDH1 produces a cancer-related accumulation of 2-hydroxyglutarate^[3]. To date, no literature data are available about the diagnostic use of this mutation to differentiate enchondroma from chondrosarcoma.

Our patient did not show recurrence or distant metastases at 18 months follow-up after surgery. She is now pain free and shows only modest strength deficit in pinching and grasping. She is able to write, study, and make housewife-related tasks independently. She showed a high grade of satisfaction for the good aesthetic and functional results achieved.

A lifelong, three-months interval follow-up has been planned, to check for local recurrence, other enchondromas malignant transformations, and occurrence of metastasis. If any of these complications would appear, amputation of the ray will be mandatory.

List of abbreviations

MRI: magnetic resonance imaging; ⁹⁹Tc: technetium 99; PCR: polymerase chain reaction; IDH1: isocitrate dehydrogenase 1; CT: computed tomography; α -KG: α -ketoglutarate; CS: chondrosarcoma.

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