

Guided Growth in Skeletal Deformity Associated with DNA-Confirmed Ollier Disease

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Abstract- Ollier disease (Spranger type I) is a rare, non-hereditary skeletal dysplasia characterized by asymmetrically distributed enchondromas. We report a case of an eight-year-old female presenting with left lower limb shortening and varus deformity. Radiographic evaluation revealed multiple osteolytic lesions typical of the disease. For the first time in early-stage diagnosis, targeted next-generation sequencing (NGS) was applied, identifying a heterozygous pathogenic IDH1 variant (c.394C>T; p.Arg132Cys), thus enabling prompt molecular confirmation. Surgical management combined guided growth via proximal tibial epiphysiodesis with intraoperative bone biopsy in a single session, reducing anesthetic exposure and hospitalization time. The early application of molecular genetic testing in this case contributed to improved diagnostic accuracy and more effective treatment planning, ultimately supporting better patient outcomes in skeletal dysplasia.

Key words: DNA analysis, Ollier, genetic, epiphysiodesis

1. Introduction:

Multiple enchondromatosis is a congenital skeletal disorder affecting children under the age of 9 years. ⁽¹⁾ The condition represents intraosseous cartilaginous tumors that evolve around the growth plate. ⁽¹⁻³⁾ The prevalence is 1/100000 of population with equal sex distribution and arise usually around the first and fourth decades of life. Studies show that this condition has the capacity to become malignant in 20-40% of all patients. The most common associations are limb-length discrepancies, spontaneous fractures, angulations and skeletal deformities that could eventually lead to gait abnormalities, limping, restricted range of motion and could drastically affect the quality of life. It is usually presented on a single side. Diagnosis is suspected after a plain radiograph of these patients and could be confirmed by DNA sequencing. Treatment options might vary and include deformity correction, rehabilitation, guided growth epiphysiodesis and radical surgery in malignant cases.

2. Case report:

The presented patient is an eight-year-old girl delivered from third normal pregnancy, weighing 2,900 grams at birth, with normal health development until May 2024, when the parents noticed a change in gait with “left limb lateralization” and upon examination limb-length discrepancy was noticed. In July 2024, total calcium, ionized calcium, phosphorus, alkaline phosphatase, 25-OH D and urine were examined and normal values were detected. **(Table.1)** In September and October a curvature of the left lower limb was reported and a shortening of 1.5 cm was measured. The child is not burdened with bone and other diseases in the family. She has a 19-year-old brother - healthy and a 15-year-old sister – with no history of diseases.

The patient was admitted in good general health with normal growth and development, unremarkable physical examination findings across all systems, and no signs of infection or pathology.

Musculoskeletal assessment revealed marked hypermobility of the elbow, wrist, and knee joints, left lower limb shortening with associated varus deformity, and lumbar sagittal plane curvature accompanied by asymmetrical waist contours and inferior positioning of the left shoulder; no pain or swelling was reported in the affected limb.

Plain radiograph shows multiple bone lesions affecting the left distal ½ tibia, left sided pelvic tilt and absolute anatomical leg-length difference of 1.5 cm. **(Fig.1)** Osteolytic lesions with well-defined sclerotic margins, endosteal erosions and ground-glass appearance of the matrix, typical for Spranger Type I multiple enchondromatosis were present. **(Fig.2)**

Considering the discrepancy and the bony pathology a decision about surgical intervention was accepted. The surgical plan included: epiphysiodesis of the right proximal tibia with 8-plate implant and bone block biopsy of the affected limb in one surgical time in order to reduce hospital stay, anesthesia time and expeditive diagnosis.

Test Name	Result	Unit	Reference Range
Alkaline Phosphatase	285.44	U/l	Up to 320.00
Iron (Fe)	13.15	μmol/l	5.50 - 18.60
Potassium (K ⁺)	4.40	mmol/l	3.50 - 5.60
Total Calcium (Ca)	2.43	mmol/l	2.20 - 2.70
Ionized Calcium (Ca ²⁺)	1.20	mmol/l	1.16 - 1.32
Anti-CCP IgG	0.60	U/ml	Up to 10.00
Anti-CCP IgA	1.80	U/ml	Up to 10.00
C-Reactive Protein (CRP)	0.65	mg/l	Up to 5.00
25-OH Vitamin D	78.40	nmol/l	50.00 - 120.00

Table. 1 Laboratory results

3. Surgical technique:

The patient was positioned supine on a radiolucent operating table with a thigh tourniquet applied, and the lower limbs were prepared for surgery under fluoroscopic guidance. The right proximal tibial physis was identified, marked, and accessed through a small incision, allowing for accurate placement of a K-wire and subsequent 8-plate fixation using two compressive screws. An identical technique was employed on the medial proximal tibial side, with implant dimensions tailored to the patient's anatomical characteristics. ⁽²⁾ During the same operative session, a lesion in the distal tibia of the left leg was located under fluoroscopy and a bone block was resected for biopsy. Post-operative care included immediate verticalization, early mobilization, and a standardized rehabilitation protocol, with radiographic follow-ups planned at three and six months, and long-term monitoring guided by ESMO recommendations to assess for malignant transformation.



Fig.1 Diagnostic imaging due to limb -length discrepancy



Fig.2 Post-operative X-ray after proximal right-side tibia epiphysiodesis

4. DNA analysis

The full coding sequence and intron/exon boundaries of the IDH1 gene were analyzed using next-generation sequencing (NGS) technology on an Ion Gene Studio S5 instrument with the Oncomine Comprehensive Assay Plus v.2.5 panel (ThermoFisher Scientific). This analysis has an analytical sensitivity of 99% and specificity of 98.3% for single nucleotide variant (SNV) detection, along with high sensitivity for copy number variant (CNV) detection and 100% specificity. In the DNA isolated from the tissue biopsy, a heterozygous pathogenic variant c.394C>T (p.Arg132Cys) in the IDH1 gene

was identified. The variant c.394C>T (p.Arg132Cys) results from an amino acid substitution at codon 132, replacing arginine with cysteine. Literature reports indicate the variant c.394C>T (p.Arg132Cys) has been identified in patients with Ollier disease and is present at a very low frequency in population databases (A=0.000007, 1/148442 in GnomAD_genomes v4, rs121913499). In silico predictive analyses classify the variant as damaging to protein structure and function across six prediction programs.

Based on this information, the c.394C>T (p.Arg132Cys) variant in the IDH1 gene is classified as pathogenic according to ACMG guidelines.

5. Discussion:

Ollier disease (Spranger type I) represents a rare skeletal disorder characterized by multiple enchondromas, typically presenting with an asymmetrical distribution predominantly affecting the appendicular skeleton.⁽³⁾ This condition is hypothesized to result from abnormal enchondral ossification, attributable either to aberrant proliferation of ectopic chondroid tissue islands or to impaired maturation of the epiphyseal growth plate, leading to excessive chondrogenic proliferation within the affected bones.⁽⁴⁾ Spranger's 1978 classification system categorizes Ollier disease based on radiographic features, anatomical location, and inheritance patterns. Ollier disease generally manifests sporadically, without familial aggregation, and the irregular lesion distribution supports the hypothesis of postzygotic somatic mosaic mutations as the underlying pathogenic mechanism.^(5,6)

Diagnosis of enchondromatosis is primarily clinical, characterized by skeletal deformities, limb-length discrepancies, angular deviations, and pathological fractures, with palpable nodules in cases involving the metacarpals.⁽⁷⁾ Clinical presentation varies by lesion size, number, anatomical location, and age at onset, with most patients initially presenting with angular deformities or limb asymmetry.⁽⁸⁾ Radiological imaging reveals homogeneously radiolucent, lytic lesions with sharply defined margins. Histopathology plays a limited role, mainly for malignancy exclusion. Recently, next-generation sequencing of enchondromatous tissue has enhanced diagnostic accuracy, offering rapid and definitive results in challenging cases.

Conservative treatment remains the primary approach for Ollier disease due to the absence of effective pharmacologic therapies⁽⁹⁾, while surgical intervention is indicated for significant limb-length discrepancies, progressive deformities, or suspicion of malignant transformation. Surgical strategies include curettage with bone grafting, corrective osteotomies, and guided growth techniques such as epiphysiodesis, which has emerged as an effective intervention for addressing growth discrepancies. Complete curettage is typically limited by lesion extent and is associated with a high risk of non-union.⁽¹⁰⁾ Limb-lengthening procedures pose complications related to osteogenesis and fracture at the corticotomy site. Given the 5–50% potential for malignant transformation, surgical intervention remains essential, though frequently associated with functional morbidity, prolonged recovery, and the necessity for long-term surveillance.⁽¹¹⁾

6. Conclusion:

This case demonstrates the diagnostic utility of next-generation sequencing in confirming Ollier disease through detection of the pathogenic IDH1 c.394C>T mutation, enabling targeted clinical management. Hemiepiphysiodesis on the right tibia effectively corrected limb-length discrepancy, while biopsy of the left distal tibial lesion facilitated histopathological evaluation and malignancy risk assessment. The integration of molecular diagnostics with anatomically precise surgical intervention exemplifies a precision medicine approach to complex skeletal dysplasias.

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Fig.2 Post-operative X-ray proximal right-side tibia epiphysiodesis

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