Ollier Disease: Pathogenesis, Diagnosis, and Management

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abstract

Ollier disease (Spranger type I) is a rare bone disease that is characterized by multiple enchondromatosis with a typical asymmetrical distribution and confined to the appendicular skeleton. The pathogenesis of enchondromatosis is not clearly understood. Recently, heterozygous mutations of PTHR1, IDH1 (most common), and/or IDH2 genes have been suggested by various authors as genetic aberrations. Genomic copy number alterations and mutations controlling many vital pathways are responsible for the pathogenesis of Ollier disease. A comprehensive description of all genetic events in Ollier disease is presented in this article. Clinically, Ollier disease has a wide variety of presentations. This article describes the plethora of clinical features, both common and rare, associated with Ollier disease. Multiple enchondromas are most commonly seen in phalanges and metacarpals. Radiologically, Ollier disease presents with asymmetrical osteolytic lesions with well-defined, sclerotic margins. In this article, various radiological features of Ollier disease, including radiographs, computed tomography, and magnetic resonance imaging, are also discussed. Gross pathology, cytological, and histological features of both Ollier disease and its malignant transformation are outlined. Although treatment is conservative in most cases, different possible treatment options for difficult cases are discussed. In the literature, there is a paucity of data about the disease, including diagnosis, management, prognostication, and rehabilitation, necessitating a comprehensive review to further define all of the possible domains related to this disease. [Orthopedics. 2015; 38(6):e497-e506.]
Chondromas are benign, generally asymptomatic tumors of hyaline cartilage that are most commonly located in the phalanges of the hand. They are called enchondromas when they arise from the medullary canal. Rarely, they arise on the surface of the bone and are referred to as periosteal chondromas or juxtacortical chondromas.

Enchondromas are the second most common benign cartilaginous tumor after osteochondromas. Enchondromatosis, or Ollier disease, is defined by the presence of multiple enchondromas (3 or more) and characterized by an asymmetric distribution of cartilaginous lesions that can be extremely variable in terms of their size, number, location, evolution, age of onset and diagnosis, and requirement for surgery. The association of lymphangiomatas with Ollier disease and Maffucci syndrome (another enchondromatosis) has been described in the literature.

**Epidemiology and Classification**

The estimated prevalence of Ollier disease is 1 in 100,000. The true incidence of Ollier disease may be higher because mild phenotypes without skeletal deformities are sometimes not detected. Few cases of familial occurrence have been reported (Table 1).

Spranger et al created a comprehensive classification of enchondromatosis based on radiographic appearance, anatomic site, and mode of inheritance. They divided enchondromatosis into 6 subtypes: type I, Ollier disease; type II, Maffucci syndrome; type III, metachondromatosis; type IV, spondyloenchondrodysplasia; type V, enchondromatosis with irregular spinal lesions; and type VI, cheirospondyloenchondromatosis. Most subtypes are nonhereditary, whereas some are autosomal dominant or recessive. Halaal and Azouz later added 3 subtypes to this classification system based on case reports of enchondromatosis: generalized enchondromatosis with irregular vertebral lesions, generalized enchondromatosis with mucopolysacchariduria, and enchondromatosis with concave vertebral bodies. The modified Spranger classification system is widely used to address types of enchondromatosis, and the common subtypes are listed in Table 2.

**Pathophysiology**

The pathogenesis of enchondromatosis is still not clearly understood. Ollier disease is basically an abnormality of development of the limb bud, which, in postfetal life, causes the long bones to grow in diameter but not in length. The modified Spranger classification system is widely used to address types of enchondromatosis, and the common subtypes are listed in Table 2.

In 1943, Jaffe and Lichtenstein proposed that enchondromatous lesions are actually the displaced cartilaginous rests of normal physeal cartilage cells. This
theory is still widely accepted regarding the genesis of enchondroma. There are formations of intraosseous cartilaginous foci in enchondromas that might result from the abnormalities in signaling pathways controlling the proliferation and differentiation of chondrocytes.24

Homozygous mutations24,25 and nonsense mutations24 in parathyroid-related peptide type 1 receptor (PTHR1) or dysregulation in the Indian hedgehog signaling pathway (eg, overexpression of hedgehog transcriptional regulator GLI2 or activation of a hedgehog-responsive GLI2-luciferase in a PTHR1 mutant25) may cause development of enchondromatous lesions in patients with Ollier disease.

Recently, homozygous mutations in the isocitrate dehydrogenase (IDH) gene have been related to Ollier disease, mainly IDH1 (98%) and IDH2 (2%).26-28 These mutations exhibited a phenomenon of intraneoplastic mosaicism similar to that seen in fibrous dysplasia and osteochondroma.26

The incidence pattern of Ollier disease is unknown but is thought to be simply a Mendelian pattern.24,31,32 Hence, it seems that Ollier disease is a manifestation of heterogeneity of various molecular defects.

**Clinical Features**

The pathognomonic features of Ollier disease are as follows:11:

1. Onset in early childhood
2. Radiological changes limited to the long ends of the bone with stripping of rarefied areas; secondary involvement of epiphysis and appearance of speckling in metaphysis and epiphysis with development of growth
3. Histological presence of cartilage in a portion of tissue taken from the radiolucent area shown on radiographs

There is a large clinical variability in the presentation of Ollier disease with respect to size, number, location, and age of onset.11-33-35 Ollier disease usually manifests in first decade of life34,36 but has also been reported in early adolescence and adulthood.37,38 These lesions usually appear and grow before puberty but soon remodel into normal bone.6,39 Whereas enchondromas occur equally in both sexes, Ollier disease is seen twice as often in men than in women.40

Patients usually present with painless bony masses (Table 4). Although lesions generally occur bilaterally, with a unilateral predominance leading to asymmetric distribution, bilateral symmetric presentation has also been described (Figure 1).41 They have a predilection for the appendicular skeleton, but the trunk bones can also be involved in severe cases.42 Enchondromas are most commonly seen in phalanges and metacarpals and are rarely seen in the carpal bones.43 Ollier disease is also frequently seen in long bones like the femur andibia. The trochanters of the femur are commonly involved, whereas the femoral neck is relatively spared.44 Slonog et al44 reported Ollier disease in the femoral neck leading to posterior tilting of the proximal femoral epiphysis mimicking slipped capital femoral epiphysis. Other bones that can be involved are the pelvis (especially the iliac crest), fibula, and humerus, but rarely are the ribs, sternum, and skull involved; characteristically the vertebral and craniofacial bones are not involved.42,45 The pelvis is the most frequently involved trunk bone, which can lead to scoliosis.7

The most common presenting symptom is cosmetic deformity due to the presence of multiple swellings on the extremity.46 Rarely, bone shortening is

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### Table 3

**Proposed Theories for the Pathogenesis of Ollier Disease**

<table>
<thead>
<tr>
<th>Theory</th>
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<tbody>
<tr>
<td>Displaced remnants of normal physeal cartilage cells18</td>
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<tr>
<td>Hamartomatous growth of cartilage cells19-21</td>
</tr>
<tr>
<td>Failure of endochondral ossification22</td>
</tr>
<tr>
<td>Migration of dysplastic nidus from physeal proliferative zone to primary ossification zone in metaphyses23</td>
</tr>
<tr>
<td>Failure of terminal differentiation of growth plate chondrocytes24</td>
</tr>
<tr>
<td>Heterozygous mutations of PTHR1 gene25</td>
</tr>
<tr>
<td>Heterozygous mutations of IDH1 and/or IDH2 gene26-28</td>
</tr>
<tr>
<td>Loss of chromosomes (Chr 6 and Chr 3), deletions, amplifications, gains, and other genomic copy number neutral structural changes of subtle genes29,30</td>
</tr>
<tr>
<td>Familial11</td>
</tr>
</tbody>
</table>

### Table 4

**Clinical Presentations of Ollier Disease**

- Multiple swellings
- Cosmetic embarrassment
- Asymmetric physeal arrest
- Madelung deformity
- Angular deformity
- Genu varum
- Genu valgus
- Cubitus valgus
- Coxa vara
- Coxa valga
- Pelvis involvement
- Obstructed labor
- Scoliosis
- Limb-length discrepancy
- Gait disturbances
- Pathological fractures
- Pain
- Loss of function
the only clinical finding. This shortening may be due to the defect in the longitudinal growth of the bones. These growth disturbances are either due to an abnormal epiphyseal plate adjacent to the enchondromas or to the tethering of the epiphyseal cartilage by an abnormally thick periosteal sleeve formed in reaction to the enchondromatous lesions. Asymmetrical prematurity of the metaphyses may lead to angular deformity. The concavity of the angular deformity is toward the extensive enchondromatous region. Widening and broadening of the metaphysis occurs as the bone starts growing transversely. As a result, deformities such as genu valgum and cubitus varus, limitations in joint mobility, and leg-length discrepancy may occur. Pathological fractures may occur due to thinning of the cortical bone over the growing lesions. Facial asymmetry and cranial nerve palsies may also occur. Neural compression is less frequently seen in Ollier disease than in hereditary multiple exostosis.

Various tumors are associated with Ollier disease (Table 5). The reported incidence of malignant transformation of enchondromas in Ollier disease ranges from 5% to 50%. Chondrosarcomas are the most common malignancy arising from Ollier disease and are present in approximately 25% of patients by age 40 years. Malignant transformation usually occurs between ages 13 and 69 years. Central chondrosarcomas, located centrally in the medullary cavity, may lead to sarcomatous changes in underlying enchondromas. The risk of sarcomatous changes of enchondromas increases in proportion to the amount of dysplastic tissue (ie, the number and size of lesions) present in the lesions and cytogenetic aberrations. An interstitial deletion of the short arm of chromosome 1 [del(1)(p11p31.2)] has been described in a low-grade chondrosarcoma developing in a patient with Ollier disease. Such deletion has also been noticed in primary chondrosarcomas. There are larger numbers of gains and losses of genomic copy numbers and their loss of heterozygosity in chondrosarcomas associated with Ollier disease than in enchondromas. They are most commonly seen in chromosomes 3p, 5q, 6q, 9p, which results in increased genetic instability. These secondary chondrosarcomas are generally grade I or II. There may also be a correlation between expression of PTHrP, PTHR1, and Bcl2 genes and the grade of malignancy in chondrosarcoma. There is an increased chance of genetic aberrations and mutations in higher-grade chondrosarcomas than in lower-grade chondrosarcomas. Chondrosarcomas resulting from multiple enchondromatosis mainly affect the pelvis, shoulder girdle, distal femur, and proximal tibia. Chondrosarcomas of the hand resulting from enchondromatosis appear to be rare. Muramatsu et al and Goto et al have reported chondrosarcomas in the hand resulting from Ollier disease, although rare, mainly toward the ulnar side.

Pain, increasing lesion size, and thinning of the cortices are typical clinical and radiological signs of transformation to low-grade chondrosarcoma. Features like size greater than 5 to 6 cm, more than two-thirds’ endosteal scalloping of the cortex, cortical breach, extraossseous soft tissue mass, marked uptake on bone scan, and periosteal reaction also suggest malignant transformation. The usual behavior of secondary chondrosarcomas in enchondromatosis is local invasion, local recurrence, and distant metastasis, most commonly to the lungs. Damron et al reported nonmonomelic, multicentric, malignant chondrosarcomas associated with Ollier disease.

INVESTIGATIONS
Radiographs

On plain radiographs, enchondromas typically appear as osteolytic lesions (medullary) with well-defined, sclerotic margins; endosteal erosion; and ground-glass appearance of the matrix (Figure 2). Channel-like radiolucent areas in the metaphysis with an “organ pipe” appearance in long tubular bones are common in Ollier disease. The lesions have punctate calcification typical of the radiographic appearance of cartilaginous matrix. Dystrophic calcification within the matrix of small cartilage masses or fragments of lamellar bone are often described as the ring and arc, flocculent, or stippled pattern of calcification commonly appreciated in long bones. Calcification denotes degeneration and poor vascularity of the lesions; therefore, densely calcified lesions accumulate less tracer on bone scan.

The bones of the hand demonstrate a characteristic globular appearance on radiographs. The radiological appearance of
enchondromas occurring in flat or irregular bone may not be diagnostic. No periosteal reaction is seen in uncomplicated enchondromas.\(^8\)

**Computed Tomography**

Computed tomography (CT) is superior to radiography in detecting matrix mineralization, calcification pattern, lobulated lesion margins, and degree and extent of endosteal scalloping (Figure 3A). This is particularly important for lesions occurring in the areas difficult to evaluate with radiographs, like the pelvis.\(^8\)

Computed tomography is also useful in evaluating the size and presence of any soft tissue component, which would favor a diagnosis of chondrosarcoma, although a soft tissue component in enchondroma may occur in association with a fracture.

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**Table 5: Tumors Associated With Ollier Disease**

<table>
<thead>
<tr>
<th>Tumor Type</th>
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<tbody>
<tr>
<td>Chondrosarcoma(^{51,64})</td>
</tr>
<tr>
<td>Osteosarcoma(^{34,65})</td>
</tr>
<tr>
<td>Central nervous system tumors</td>
</tr>
<tr>
<td>Chondrosarcoma-like parasellar chondrosarcoma</td>
</tr>
<tr>
<td>Glioma, glioblastoma multiforme(^66)</td>
</tr>
<tr>
<td>Astrocytoma(^51)</td>
</tr>
<tr>
<td>High-grade anaplastic astrocytoma(^65,67)</td>
</tr>
<tr>
<td>Oligoastrocytoma(^43)</td>
</tr>
<tr>
<td>Oligodendroglioma(^32)</td>
</tr>
<tr>
<td>Ovarian tumors</td>
</tr>
<tr>
<td>Juvenile granulosa cell tumor(^{51,68-73})</td>
</tr>
<tr>
<td>Sertoli-Leydig cell tumor(^74)</td>
</tr>
<tr>
<td>Leukemia</td>
</tr>
<tr>
<td>Chronic myeloid leukemia(^75)</td>
</tr>
<tr>
<td>Acute myelogenous leukemia(^31)</td>
</tr>
<tr>
<td>Breast adenoma(^74)</td>
</tr>
<tr>
<td>Lung tumor</td>
</tr>
<tr>
<td>Non-small-cell lung cancer(^76)</td>
</tr>
<tr>
<td>Fibromatosis (deep)</td>
</tr>
<tr>
<td>Extra-abdominal desmoid tumor(^77)</td>
</tr>
</tbody>
</table>

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**Figure 2:** Anteroposterior radiographs of both hands (A), fingers (B), wrist (C), leg (D), and feet (E) showing multiple well-defined, expansile lytic lesions involving the metacarpals, metatarsals, phalanges, distal end of the radius and ulna, and lower end of the tibia/fibula. No matrix mineralization is seen.

**Figure 3:** Coronal reconstructed computed tomography scan (A) and T2-weighted magnetic resonance image (B) of the right hand confirming the presence of multiple well-defined cystic lesions. No associated soft tissue component is seen. Lesions show hyperintense signal on the T2-weighted image.
and hematoma. Recently, 3-dimensional reconstructed CT has provided help in surgical planning for patients with Ollier disease.  

**Magnetic Resonance Imaging**

Magnetic resonance imaging (MRI) may be requested in cases of pathological fracture when lesional characterization is necessary prior to treatment. On MRI, the nonmineralized component of enchondromas appears as low to intermediate signal intensity lesions on T1-weighted sequences and intermediate to high signal intensity lesions on T2-weighted sequences (Figure 3B). Small speckled foci of high signal intensity, often evident on T1-weighted MRIs, are postulated to be due to the lobular growth of enchondromas, which leaves intervening residual areas of normal yellow bone marrow. Low signal intensity septa on T2-weighted MRIs are also evident, corresponding pathologically to chondral ossification or fibrous septations. Following contrast administration, enchondromas exhibit central ring and arc enhancement and septal and peripheral rims of enhancement. This pattern of enhancement is also seen in chondrosarcomas. Preliminary studies performed with dynamic MRI have suggested early enhancement of chondrosarcoma as a possible useful differentiating feature.

**Bone Scintigraphy**

The most common bone scintigraphic finding is increased uptake in the long bone diaphysis or metaphysis. Pinhole scintigraphy is helpful in determining the metabolic profile of the tumor tissue in its different evolutionary stages. Enchondromas may show high uptake on fluorodeoxyglucose–positron emission tomography (FDG-PET) and can sometimes mimic a metastatic lesion in a patient being screened for metastasis. Bone scan is also helpful in detecting and screening malignant transformation like chondrosarcoma because the majority (82%) of long-bone chondrosarcomas reveal intense uptake on bone scans, whereas long-bone enchondromas show mild to moderate increased radiotracer activity in only 21% of cases. In addition, a heterogeneous pattern of uptake is seen in 63% of long-bone intramedullary chondrosaromas vs 30% of enchondromas. Tc-99m (V) DMSA scintigraphy can also be used and may be superior to Tc-99m MDP scintigraphy for distinguishing benign and malignant chondrogenic tumors, as well as being useful in predicting malignant transformation of chondrogenic tumors.

**Pathology**

Macroscopic examination of enchondromas usually shows multiple oval-shaped or round cartilaginous nodules, limited at their periphery by woven or lamellar bone and separated from each other by intertrabecular marrow spaces in the solid cartilaginous matrix with myxoid changes appearing as fraying of the matrix. Microscopically, there are sharply demarcated lobules of mature, hypocellular hyaline cartilage with few double-nucleated cells without cytologic atypia (Figure 4); however, cellularity of the tumor may vary with increased mitosis. Inside a network of trabecular bone, islands of mature, nonvesiculated hyaline cartilage cells of various sizes and shapes are embedded in abnormally dense metachromatic staining extracellular substance. The matrix does not show any myxoid change. Calcification and ossification are common, especially at the periphery of cartilage lobules. This characteristic pattern is called bone encasement.

**Cytology**

Needle cytology is instrumental in making the diagnosis of Ollier disease. Anshu et al reported Papanicolaou stained smears showing the presence of numerous cartilaginous fragments with angular edges. Singly scattered round cells were also present, occasionally in tight clusters. The cells had eccentrically placed round nuclei and abundant pale cytoplasm.

Binucleation, mild atypia, hypercellularity, and large plasmacytoid nuclei, which would indicate malignancy in a solitary cartilaginous tumor, are acceptable features for benign enchondromas in multiple enchondromatosis. It is difficult to differentiate enchondromas from grade I chondrosarcomas until, in the latter, the characteristic bone marrow permeation with trapping of host lamellar bone on all sides is seen.

**Differential Diagnosis**

Ollier disease must be differentiated from multiple hereditary exostosis. The most important criterion to distinguish enchondromas from osteochondromas as seen in multiple hereditary exostosis is the localization of bone lesions: osteochondromas are located at the bone surface and enchondromas are located in the center of bones, thus allowing radiographic distinction.

Radiologically, Ollier disease may mimic osteitis fibrosa cystica.

**Treatment**

Treatment of Ollier disease is usually conservative, unless complications occur. The lesions can be left untreated because functional impairment is usually not severe. Surgery is performed in cases of deformity, limb-length discrepancy, pathological fracture, and malignant transformation.

The important goals of the treatment are as follows:

1. Achieving mechanical alignment
2. Achieving equivalent limb length for normal walking
3. Relieving pain from a pathological fracture

Treatment is directed toward the more extensively involved limb, deformities, and complications. Shapiro reported that an angular deformity greater than 25° that is not balanced by reverse deformity is an indication for surgery.

Only a few treatment options are available for Ollier disease, especially for im-
proving appearance. An oft-used modality is intralesional curettage with or without bone grafting and/or artificial bone substitute, various osteotomies, and internal fixations. These treatments do not address the problem of limb-length discrepancy. Adas et al. showed good results with curettage and cementing in distal femur affected with Ollier disease. Osteotomy has been used, but it must be repeated many times. Also, the presence of weak bones is a problem that makes internal fixation difficult. Other modalities of surgical treatment follow.

**Ilizarov Technique**

The Ilizarov technique is difficult but effective in providing mechanical stabilization in patients with Ollier disease. Distraction osteogenesis enhances the conversion of abnormal cartilage of the lesion into new lamellar bone, without the need for intralesional curettage or bone grafting, which was proved radiographically by Jesus-Garcia et al. Tellisi et al. used a multiaxial correction frame for distraction osteogenesis in a humerus affected by Ollier disease.

More wires and olive wires are required for the stabilization because the bones are weak and many enchondromas are present.

**Intramedullary Nailing**

Intramedullary nailing is used in patients with limb-length discrepancies. García-Cimbrelo et al. used an intramedullary elongation nail for femoral shortening when performing intramedullary osteotomy (internal osteotomy) followed by distraction followed by intramedullary nailing. This allows a shorter treatment time and early removal of the external fixator to prevent pin-tract infections and intramedullary infections; it also prevents complications like fracture, deformity, shortening, and nonunion arising from premature removal of the external fixator. Baumgart et al. described good results in 12 patients using intramedullary nailing with a special motorized sliding mechanism.

**Corticoplasty and Diaphysectomy**

Partial resection of the cortical bone with curettage of the tumor (corticoplasty) for treating hand deformity in Ollier disease has been performed by Kim et al. They concluded that corticoplasty resulted in cosmetic improvement without functional deterioration.

Total/subtotal diaphysectomy and reconstruction with structural autografts or allografts are usually performed for the treatment of extensive enchondromas involving the fingers. Amputation/Limb Salvage

Although ray amputation can be performed for Ollier disease of the hand depending on the severity of involvement (eg, when destruction of cortical bone and larger lesions are present), limb salvage can be performed in a severely affected hand because, despite large bony deficits after the first resection, bony regrowth can occur without the need for bone autograft.

**Rehabilitation**

Physiotherapy like ultrasound, cryotherapy, CO₂ laser with stretching, active mobilization, occupational therapy, and coordination exercises improve the functional ability of patients with Ollier disease.

**Prognosis**

Because widely distributed enchondromas may pose fewer problems than localized ones (eg, limb shortening, asymmetry), it is difficult to assess the prognosis of Ollier disease (Table 6). Multiple enchondromas in Ollier disease have an increased rate of recurrence after surgery, so aggressive follow-up should be performed in these cases.

Annual surveillance of patients with Ollier disease, both children and adults,
is recommended. Periodic surveillance of the brain and abdomen for occult lesions should also be performed in these patients.

**CONCLUSION**

Ollier disease is a rare disorder characterized by asymmetrical and bilateral painless bony lesions mainly confined to the appendicular skeleton. The disorder commonly presents with cosmetic deformity, limb-length discrepancy, and pathological fractures, and it is associated with various tumors, especially chondrosarcomas. Ollier disease must be differentiated from other causes of multiple bony swellings. Given the hypercellularity of enchondromas in Ollier disease, histological distinction between benign and malignant tumors may be difficult; therefore, in suspected malignant transformation, dynamic MRI and bone scan may help the diagnosis, in addition to commonly used investigations like radiographs and CT. The treatment of Ollier disease is usually conservative; however, in some complicated cases, reconstructive surgery after excision to amputation can be performed. The overall prognosis of Ollier disease is favorable, but annual surveillance in children and adults is recommended.

**REFERENCES**


Table 6

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<td><strong>Malignant transformation</strong></td>
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