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Case Report

Ollier disease: two case reports and a review of the literature

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Abstract: Ollier disease is a rare tumor with unclear clinicopathological features and pathogenesis. We herein report two cases of Ollier disease in a 15-year-old boy and a 66-year-old man. We analyzed the clinicopathological, radiographical, and histochemical characteristics of Ollier disease in these two cases. Furthermore, we reviewed the literature to better understand the clinicopathological features of this disease. The boy had multiple enchondromas in the metaphysis and upper region of the left femur, and his left leg is short naturally. The 66-year-old man had multiple enchondromas in his left ribs and lower segment of the left femur. He was sent to the hospital because of pathological fracture of the ribs. In addition, he was diagnosed with gastric cancer 4 years before visiting an orthopedic clinic. Ollier disease is a rare bone disease that often renders a typical asymmetrical distribution and is confined to the appendicular skeleton. It is known as a benign bone tumor and has a high risk of malignant transformation into a chondrosarcoma (5%-50%). Correct diagnosis requires radiographic, histochemical, and morphological analyses. Better understanding of the clinical manifestations and pathological features can improve the diagnosis and prevent malignant transformation and deformity, especially in adolescent patient.

Keywords: Ollier disease, radiography, histochemistry, diagnosis

Introduction

Ollier disease is a rare benign bone disease that often renders a typical asymmetrical distribution and is confined to the appendicular skeleton. The estimated prevalence of Ollier disease is approximately 1 in a population of 100000 [1]. It is a known non-hereditary disease with a high risk of malignant transformation into chondrosarcoma. Previous reports revealed that the incidence of malignant transformation is 5%-50% [2-5]. The genetic mechanism of Ollier disease and its malignant pathogenesis are under investigation [6]. Ollier disease is treated conservatively. When complications exist [7], the traditional surgery is intralesional curettage, which aims to avoid malformation or improve appearance. In this study, we present two typical cases with radiographic and pathological examinations and reviewed the literature to better understand the clinicopathological features of Ollier disease.

Clinical report

First case

Symptoms: A 15-year-old boy complained of progressive limping for 1 month and presented to the orthopedic clinic in October 2017. His parents recount that he has been limping since birth. Recently, he felt that this symptom was becoming severe.

Clinical examination findings: The general physical examination was remarkable for an apparent shortening of the left leg (**Figure 1A**, **1B**). We conclude it as congenital malformations. Notably, we had not touched the obvious swellings. Plain radiography showed a capsule-like radiolucent area in the metaphysis of the left femur. Computed tomography (CT) showed medical osteolytic eccentric destruction on the left femur, worm-like changes of the lesion, thinner juxtacortical area, and round transparent shad-

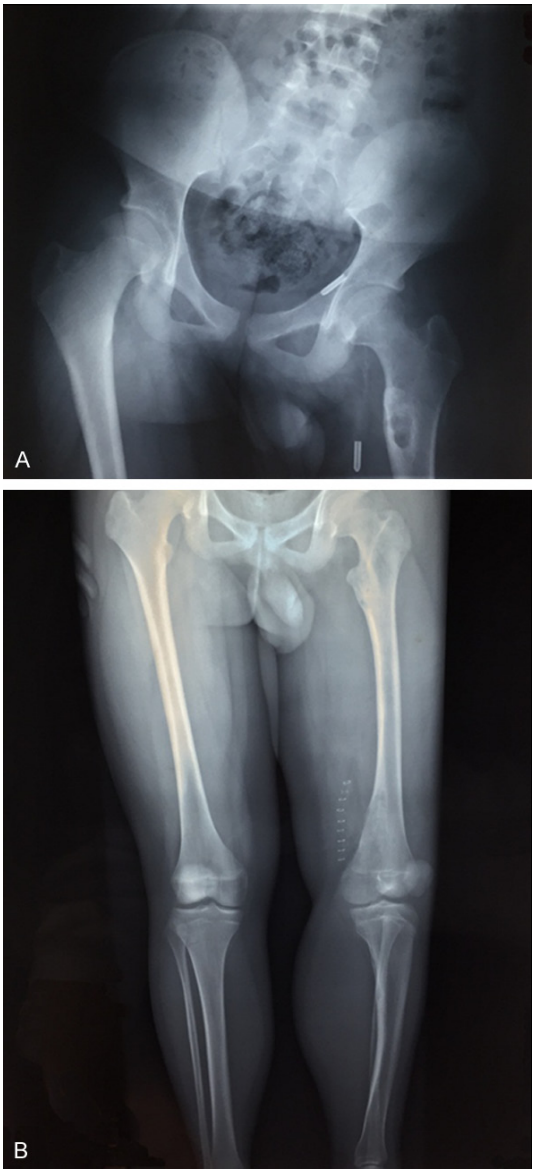

Figure 1. Anteroposterior radiograph of the pelvis (A), which shows low density of oval cavity expansion with standard, did not break the cortical bone. Hardened edge can be seen which shows a slight uneven thickness, on the right side of hardened edge of the image is not the standard, the central light in the background can be seen thin flocculent shadow. The other side of the hardened edge is not obvious. Anteroposterior radiograph of lower limbs (B) showing the medullary cavity of the left femur with cortical thinning, and pus can be seen as pale fluffy shadow. Left femur was significantly shorter than the right, and the lower 1/3 segment is thickening.

ow in the left tibia (**Figure 2A**, **2B**). Magnetic resonance imaging (MRI) showed an oval irregular low signal in the upper of left femur (**Figure 3A-C**).

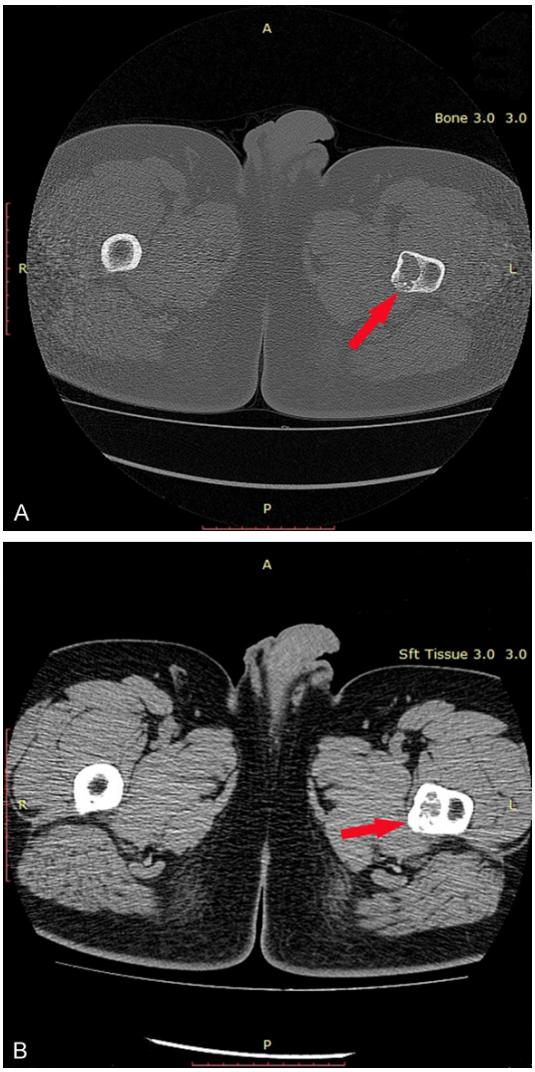

Figure 2. Computed tomography of bone (A) showing irregular low-density shadow in the medullary canal of the left femur, which is shaped as an arc or ring of high signal with stippled calcification. Computed tomography of soft tissue (B) showing no abnormal surrounding of soft tissue.

Lab findings: Leucocyte and neutrophils are significantly increased, ionized calcium reduced, and other lab findings, such as phosphorus and hydrocarbonate, had changes when he first visited our hospital (**Table 1**).

Treatment: After communicating with the patient and his parents, we performed surgery to improve his condition: curettage was performed on lesions confined proximal to the condyle of the femur combined with medullary cavity inactivation, intramedullary nail fixation, and allogenic bone graft. Intraoperatively, the lesion

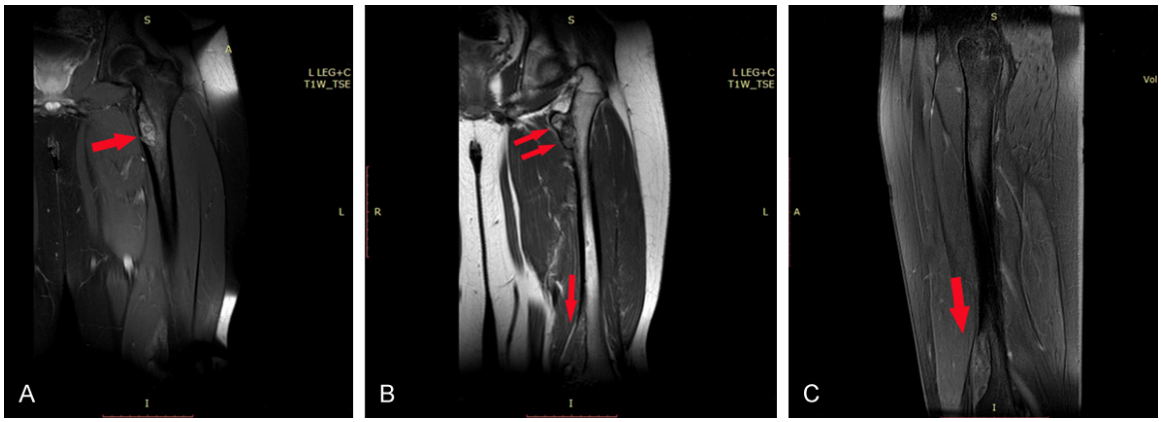

Figure 3. Magnetic resonance imaging T1-weighted coronal scan (A, B) showing the upper left femur, which demonstrates an oval irregular low signal and the lower segment with irregular flow of low signals. T1-weighted sagittal image (C) showing low signal area in the lower 1/3 and arc-and ring shadow of low signal.

Table 1. Results of laboratory investigation of the 15-year-old boy

Variable		Up or Down	Value	Reference
Blood cell data	Leucocyte (10^9/L)	↑	10.93	3.5-9.5
	Neutrophils (10^9/L)	↑	7.09	1.8-6.3
	Lymphocyte (10^9/L)	z	3.07	1.1-3.2
	Eosinophil (10^9/L)	z	0.16	0.02-0.52
	Basophil (10^9/L)	z	0.00	0.00
	Monocyte (10^9/L)	z	0.57	0.1-0.6
	Monocyte (%)	z	5.2	3-10
	RBC (10^{12}/L)	z	4.63	4.3-5.8
	Hemoglobin (g/L)	z	135	130-175
	Hematocrit (L/L)	↓	0.393	0.4-0.5
	RDW-CV (%)	z	12.0	11-15
	RDW-SD (%)	↓	36.9	37-54
	Platelet (10^9/L)	↑	441	125-350
	MPV (fL)	↑	12.7	5.0-11.0
	PCT (ml/L)	↑	0.56	0.11-0.32
	P-LCR (%)	↑	46.8	13-43
	RET (10^{12}/L)	z	0.049	0.024-0.084
	RET (%)	z	1.07	0.5-1.5
	IRF (%)	↑	6.70	0-0
Electrolyte	ICA (mmol/L)	↓	1.07	1.1-1.34
	P (mmol/L)	↑	1.80	0.85-1.51
	TCO_2 (mmol/L)	↑	30.0	22-29
	MUCS (mmol/L)	↑	84	0-28

ICA, ionized calcium; IRF, immature reticulocyte ratio; MUCS, mucous silk of urine sediment; MPV, mean platelet volume; P, inorganic phosphorus; PCT, plateletcrit; P-LCR, large platelet ratio; RBC, red blood cell; RDW-CV, red blood cell distribution width-coefficient of variation; RDW-SD, red blood cell distribution width-standard distribution; RET, reticulocyte count; TCO_2, hydrocarbonate.

sizes were 2.0×1.5 cm in the proximal and 4.0×1.5 cm in the distal of left femur.

Pathologic findings: On general observation, scratched organization was off-white gravel-like transparent tissue. The tissues were fixed in 10% buffered formalin and embedded in paraffin. Histological sections were created and stained with hematoxylin & eosin (H&E). The representative micrographs of Ollier disease are shown in **Figure 4A-D**. By combining pathologic findings of the two samples with radiographic findings, we diagnosed it as Ollier disease.

Follow-up: As of this writing, his leg discrepancy has remained stable. To correct valgus deformity, he will undergo a hemiepiphysiodesis of the distal left femur.

Second case

Symptoms: A 66-year-old male patient presented to our outpatient clinic in June 2012 with a 2-month history of painless swelling in the distal left femur. Moreover, he had multiple fracture limbs due to a collision accident. His medical records showed that he was diagnosed with gastric adenocarcinoma in August 2008, and pancreatic cancer was confirmed by

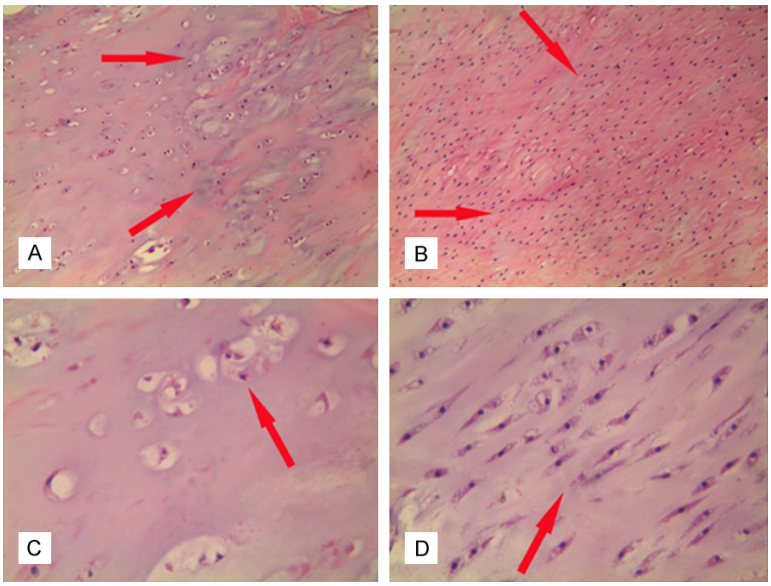

Figure 4. Histopathology of enchondroma with H&E stain (magnification ×100, A, B) showing lobulated mature hyaline cartilage (magnification ×400, C, D) showing double-core cells with a slight cytological atypia.

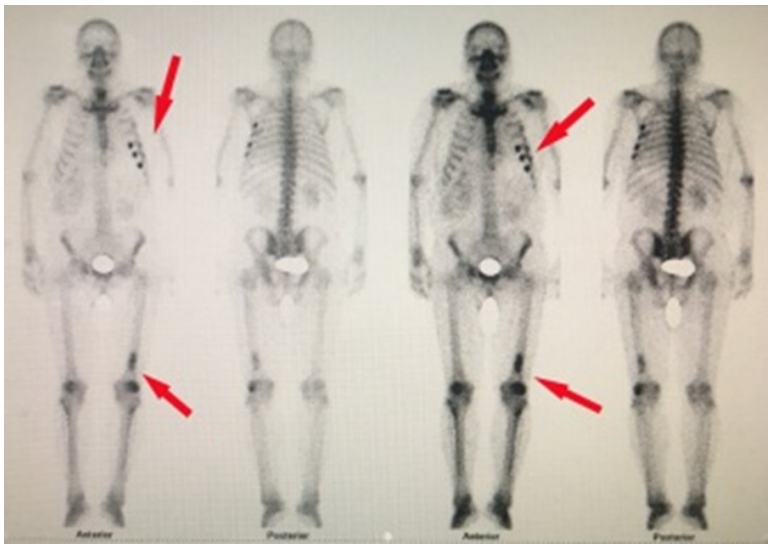

Figure 5. Three hours after intravenous injection of imaging agent, a whole-body planar scan (ECT) was performed: whole body imaging was clear, abnormal radioactive concentration was observed in the left femur, and multiple ribs on the left were beaded with sample-like radioactive concentrations.

a pathological biopsy performed in March 2015.

Physical examination findings: In June 2012, a mass in the distal left femur was found without tenderness. Local hospital record showed low-density bone destruction and bone thinning in the left femur of 6 cm long. Technetium-99m methylene diphosphonate whole-body bone scintigraphy showed abnormal radioactive concentration in the lower segment of the left femur and beaded-like radioactive concentration in various ribs, with involvement of the entire left side (**Figure 5**). Consequently, we treated him with intralesional curettage and allogeneic bone graft.

Lab findings: Blood cell data were collected by his first visit to our hospital in 2012. Monocyte and red blood cells were significantly changed. Biochemical data were collected in October 2015 after completing the chemotherapy. Tk1 (thymidine kinase 1), CA19-9 (cancer antigen 19-9), and AFU (α-L-fucosidase) were significantly increased (**Table 2**).

Treatment: Intralesional curettage and allogeneic bone graft was performed on the patient. The nail was set in the medullary cavity, and an allogenic bone was implanted. During the surgery, a bone window was made separately in the left anterolateral femur and in the pear-shaped fossa. A gray-white sand tumor-like tissue can be observed.

Pathologic findings: Scratched organization from both the lower segment of the left femur and distal left femur resembled white bone wax. Intraoperative frozen pathology showed cartilage-derived tumors, which tend to endogenous chondroma (**Figure 6A**). The remaining tissues were fixed in 10% buffered formalin and embedded in paraffin. Then, the tissues were decalcified sufficiently for 72 hours in a decalcified solution containing 10% nitric acid and 90% formaldehyde and then flushed with water after 24 hours. Histological sections were created and

Table 2. Results of laboratory investigation of the 66-year-old male patient

Variable		Up or Down	Value	Reference
Blood cell data	Leucocyte (10^9/L)	z	4.8	3.5-9.5
	Neutrophils (10^9/L)	z	2.63	1.8-6.3
	Lymphocyte (10^9/L)	z	1.45	1.1-3.2
	Eosinophil (10^9/L)	z	0.1	0.02-0.52
	Basophil (10^9/L)	z	0.00	0.00
	Monocyte (10^9/L)	↑	0.61	0.1-0.6
	Monocyte (%)	↑	12.7	3-10
	RBC (10^{12}/L)	↓	3.85	4.3-5.8
	Hemoglobin (g/L)	↓	104	130-175
	Hematocrit (L/L)	↓	0.345	0.4-0.5
	RDW-CV (%)	↑	18.7	11-15
	RDW-SD (%)	↑	61.1	37-54
	Platelet (10^9/L)	z	133	125-350
	MPV (fL)	z	10.8	5.0-11.0
	PCT (ml/L)	↓	0.1	0.11-0.32
	P-LCR (%)	z	33.9	13-43
	RET (10^{12}/L)	z	0.061	0.024-0.084
	RET (%)	↑	1.58	0.5-1.5
	IRF (%)	↑	19.20	0-0
Biochemical data	Tk1 (pm)	↑	11.12	0-2.0
	CA19-9 (IU/mL)	↑	56.39	0-37
	HPUD		Positive	Positive
	TBA (μmol/L)	↑	12.4	0-10
	PA (mg/L)	↓	76	150-400
	ALB (g/L)	↓	38.3	40-55
	GLB (g/L)	↑	41.1	20-40
	A/G	↓	0.9	1.2-2.4
	AG (mmol/L)	↓	6.0	8-16
	HDL (mmol/L)	↓	0.50	1.04-1.66
	RBP (mg/L)	↓	10.7	25-70
	AFU (μ/L)	↑	49	10-35
	m-AST (%)	↑	30.3	0-10

AFU, alpha-L-fucosidase assay; AG, anion gap; ALB, albumin; CA19-9, cancer antigen 19-9; ICA, ionized calcium; GLB, globulin; HDL, high-density lipoprotein; IRF, immature reticulocyte ratio; MUCS, mucous silk of urine sediment; MPV, mean platelet volume; P, inorganic phosphorus; PA, prealbumin; PCT, plateletcrit; P-LCR, large platelet ratio; RBC, red blood cell; RBP, retinol-binding protein; RDW-CV, red blood cell distribution width-coefficient of variation; RDW-SD, red blood cell distribution width-standard distribution; RET, reticulocyte count; TBA, total bile acid; TCO_2, hydrocarbonate.

stained with H&E. Pathological imaging is shown in (**Figure 6B**). Combined with his imaging performance, we retrospectively diagnosed it as Ollier disease.

Follow-up: The patient has recovered well after surgery. Until the final follow-up in October 2015, there was no evidence of local recurrence and/or metastasis.

Discussion

Enchondromas is a benign cartilage tumor most commonly located in the little finger (65%) and proximal phalange (60%) [8]. Some scholars thought that multiple enchondromas (enchondromatosis) is similar to Ollier disease. However, according to the World Health Organization classification of Soft Tissue and Bone in 2013, multiple enchondromas include Ollier disease and Maffucci syndrome [9]. Spranger et al. divided enchondromatosis into six subtypes based on the radiographic appearance, anatomic site, and mode of inheritance [10]. Ollier disease is classified as Spranger type I. Clinical features included multiple enchondromas of tubular and flat bones and predominantly unilateral.

Three components should be considered in the diagnosis of Ollier disease: clinical description, radiographic finding, and pathologic imaging. Radiography is highly important in the evaluation of treatments and follow-up prognosis [1]. Histological features have limited influence and are mainly used once malignancy is suspected. The diagnosis is mainly based on clinical and radiologic evaluations. Actually, intraoperative frozen pathology is inaccurate, and differential diagnosis from chondroma and chondrosarcoma is difficult.

Given the differential diagnosis from Maffucci syndrome, which is another type of multiple enchondromatosis, multiple enchondroma is

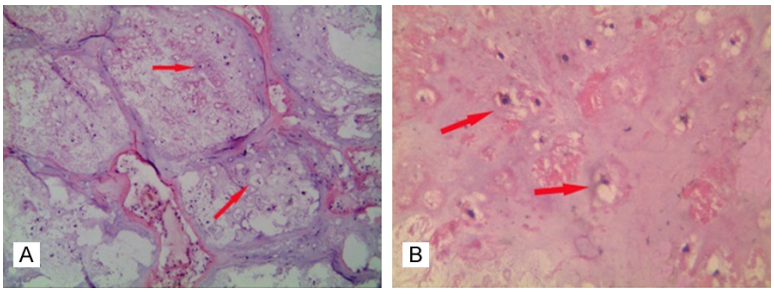

Figure 6. Intraoperative frozen section cytology showing (magnification ×400, A) lobules of mature hyaline cartilage. Histopathology of enchondroma with H&E stain showing (magnification ×400, B) mature hyaline cartilage lobules.

accompanied with soft tissue hemangiomas and occasionally lymphangiomas [11]. It is believed that these two conditions were stages of the progression to Ollier disease. Given that benign enchondromas are slow growing, hemangiomas only occur when inducing factors appear, and this concept is still not yet investigated.

Ollier disease involves short tubular bone of the hand mostly, followed by the femur, tibia, fibula, humerus, radius, and ulna [8]. Enchondromas can be in various sizes, location, number, age of onset, and diagnosis. It is a typical form of chondrosarcoma. Skeletal abnormality such as bending, shortening, pathological fracture, and asymmetric deformity can be seen in affected patients. These patients are generally first observed with angular deformity or growth discrepancy when they were still children, which peak before 10 years of age. In adult cases, multiple enchondromas can result in skeletal problems such as arthritis, deformity, or malignant transformation [4]. The aforementioned two cases both met these descriptions.

In recent years, Ollier disease was reported to occur in the pelvis, blood system, juvenile granulosa cell tumor, and cranial gliomas [12-19]. Pancreatic, liver, and breast cancers are also associated with Ollier disease, suggesting that there could have an relationship between the onset of pancreatic cancer and Ollier disease [3, 20]. Moreover, ovarian sex cord tumor was reported as an Ollier disease [21]; whether it is accurate is still controversial. Patients with enchondromas in the pelvis had a 4.8-fold higher risk of developing chondrosarcomas than those with enchondromas anywhere in the skeletal system [3]. Bone scintigraphy is the best tool for detecting multiple lesions and malignant transformation [22]. Plain radiography can diagnose separate enchondromas with typical features of a well-defined central transparent [23], sometimes with speckled, calcification in the diaphysis or metaphysis, which denotes degeneration and poor vascularity of the lesions [2]. Channel-like radiolucent areas in the metaphysis with an "organ pipe" appearance in long tubular bones are common in Ollier disease. Mineralization occurs frequently in the lesions which resembles an arc and ring.

CT is useful in evaluating the size and presence of soft tissue components [24], specifically indicated in evaluation of areas where radiography is impossible, such as the pelvis. The pattern of mineralization required high attention in predicting malformation into chondrosarcoma. Both cortical destruction and soft tissue extension were present [25]. MRI has limited application in the diagnosis of enchondromas and chondromas. Calcification of enchondromas showed lower signal intensity area in T1-weighted and T2-weighted imaging. Fibrous septations have similar manifestations. Emission CT showed abnormal radioactive concentration prompting pathological fracture or osteogenesis. ECT is useful in systemic assessment of multiple lesions with significant reference significance to Ollier disease. In recent years, positron emission tomography used in the analysis of enchondromas indicated a mild 18F-fluorodeoxyglucose uptake [26].

To date, no hereditary evidence suggests the occurrence of Ollier disease. Reported cases are distributed. Pathogenesis recognized by most scholars is failure of endochondral ossification, and this is the reason why Ollier disease in teenagers easily leads to malformation and deformity [27]. Solitary enchondromas occur in patients age 10-40 years [1], and 75% of cases happened before age 20 years. Pansuriya et al. reported about the genetic evidence of somatic mosaic isocitrate dehydrogenase 1 (IDH1) and isocitrate dehydrogenase 2 (IDH2) mutations in Ollier disease [28]. DNA sequencing demon-

strated identical IDH1 mutations in both secondary chondrosarcoma and pituitary adenoma [29]. The IDH1 and IDH2 mutations are remarkably specific to single codons: the conserved and functionally important Arg132 residue in IDH1 and the Arg172 residue in IDH2 [30]. These mutations might represent early postzygotic genetic events and account for the initiation of the disease process [31].

A previous, report revealed that *PTH1R* gene is the cause of Ollier disease. Genetic expression arrays of PTH1R in POU5F1, ANKS1B, FAM86D, and PRKG1 were changed [2]. However, in subsequent studies, it turns out that PTH1R is not the probable cause but only contributes to the occurrence of Ollier disease [32]. Increased number of genetic alterations and loss of heterozygosity were found in Ollier chondrosarcomas, which mainly involve chromosomes 9p, 6q, 5q, and 3p, and this support the view of multistep model for chondrosarcoma development. Immunohistochemistry showed that 30% of Ollier tumors are positive for protein expression of NIPBL, and POU5F1 was absent based on limited cases [2].

When malignant transformation is suspected, a biopsy should be completed. Needle cytology is instrumental in the diagnosis. What we have were intraoperative pathologic findings, which are less accurate and sensitive than biopsy. With the development of puncture technique, biopsy should be universal and convenient. Specifically for children, detecting Ollier disease as early as possible is important to prevent malformation and discrepancy as well as malignant progression into chondrosarcoma. Treatment options for Ollier disease are limited. Patients with complications such as fractures, loosening, and infection can undergo surgery, especially for improving appearance [24]. Curettage and bone graft, replacement of cortical window piece, and calcium phosphate cement are recommended alternatives. The decisive factor for successful treatment is complete curettage of the tumor [33]. Patients with malignant transformation into chondrosarcoma often need second surgical treatment, resulting in poor functional outcome and prolonged hospital stay. Once enchondroma occurs in the hand, which is common for Ollier disease, preoperative stiffness is statistically significant in affecting satisfactory outcomes. Hence, it is important to perform tenolysis at the same time with tumor curettage [8].

Enchondromas in Ollier disease tend to progress into chondrosarcomas. For grade 1 chondrosarcoma, intralesional resection is also suitable, providing lower complications and better functional outcome without significant increase in the risk of recurrence and metastasis [34]. Nursing care plays a vital role in patients with Ollier disease. Long-term care must also include monitoring patients for possible malignant changes [35].

Conclusion

Ollier disease is a rare tumor, and its clinicopathological features and pathogenesis are still controversial. As the number of reports and studies is gradually increasing, diagnosis based on pathologic features are becoming clearer, and gene mutation analyses are becoming more accurate, which may provide information of appropriate treatment, thereby preventing malformation enchondromas. These findings help patients to obtain pre-diagnosis and better therapy outcome.

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Disclosure of conflict of interest

None.

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