Idiopathic Multicentric Osteolysis: Upper Extremity Manifestations and Surgical Considerations During Childhood

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Purpose Idiopathic multicentric osteolysis (IMO) is an uncommon disease presenting during childhood with resorption of the carpus and tarsus with nephropathy. The few case reports and literature reviews do not focus on the upper extremity disease manifestations or surgical treatment options. We review our experience with the upper extremity in IMO.

Methods We evaluated 8 affected children, specifically assessing early disease manifestations, misdiagnoses, radiographic progression, and surgical treatments rendered.

Results Wrist pain and swelling are typically the first manifestations of IMO. Characteristic upper extremity findings, once the disease has progressed, include metacarpophalangeal joint hyperextension, wrist ulnar deviation and flexion, and loss of elbow extension. Radiographically, there is osteolysis of the carpus and proximal metacarpals with resorption of the elbow joint in some patients. Surgical treatments, including soft tissue release with pinning or joint arthrodesis, may offer pain relief and improve alignment, but outcomes are inconsistent.

Conclusions Children with IMO are almost always misdiagnosed initially, and the correct diagnosis may be delayed by years. The hand surgeon is ideally suited to provide an accurate diagnosis of IMO, because wrist pain and swelling and thumb interphalangeal joint contracture are common early manifestations. *(J Hand Surg 2012;37A:1677–1683.*

Type of study/level of evidence Prognostic IV.

Key words Multicentric osteolysis, wrist, surgery, idiopathic, juvenile rheumatoid arthritis.

IDIOPATHIC MULTICENTRIC OSTEOLYSIS (IMO) is characterized by progressive destruction of the carpal and tarsal bones during childhood, followed by nephropathy.[1,2] In 1937, Froehlich and Corret[3] reported carpal osteolysis in an 18-year-old woman whose disease process began at 2.5 years of age. The report contained few other details and was the first of several reports that provided limited clinical and radiographic findings.[4–19] Idiopathic multicentric osteolysis typically occurs sporadically, although it may be transmitted as an autosomal dominant disorder.[20] In 2012, Zankl et al[21] reported heterozygous mutations that clustered within the amino-terminal transcriptional activation domain of v-*maf* musculoaponeurotic fibrosarcoma oncogene homolog B MAFB, causing IMO. Soon afterward, we confirmed their finding of heterozygous mutations in our IMO patients.[21] Numerous terms have been used for IMO, including *hereditary osteolysis of carpal bones with nephropathy* (Online Mendelian Inheritance in Man-OMIM number 166300)[1] and *multicentric carpal tarsal osteolysis with and without nephropathy*.[2]

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TABLE 1. Patient Demographic Data

Patient	Age (y) at Last Follow- up	Age (mo) at Presentation	Age (y) at Diagnosis	Initial Symptom	Surgical Site
1	10	36	5	Decreased motor skills	Wrist joint
2	9	24	2	Long finger flexion posture	MCP joints
3	7	9	4	Thumb interphalangeal joint flexion posture	MCP joints
4	25	Unknown*	Unknown*	Unknown*	Wrist joint
5	9	18	8	Painful limb with ambulation	MCP joints
6	8	14	1	Wrist pain	
7	24	15	5	Wrist pain	
8	25	24	5	Painful limb with ambulation	
Average	14.6	18	4		

*The patient was adopted.

Idiopathic multicentric osteolysis has an onset in early childhood, commonly presenting with swelling and pain of the wrists and ankles.[22,23] Radiographic studies demonstrate progressive disappearance of the carpals and tarsals.[23] Idiopathic multicentric osteolysis progresses during growth, but at skeletal maturity becomes quiescent. However, the destructive nature of the disease causes permanent deformity and subsequent functional impairment.[11,23–25] There is no established medical therapy. Renal disease, confirmed by proteinuria, is commonly present in IMO, but patients with other osteolysis syndromes do not necessarily have kidney disease.[26]

We reviewed our experience with the upper extremity manifestations of IMO in 8 children, to better characterize the clinical presentation and surgical considerations.

MATERIALS AND METHODS

After institutional review board approval, we reviewed the database at Shriners Hospital for Children Saint Louis for children with a diagnosis of IMO. We identified 7 patients and included 1 additional patient from another pediatric orthopedic hospital. The 7 patients at our hospital had been followed up regularly in the Upper Extremity Surgery Clinic and Center for Metabolic Bone Disease and Molecular Research. For the 6 patients from whom we had DNA samples, we identified a heterozygous mutation in MAFB.[21]

There were 4 boys and 4 girls. The patients lived throughout the United States and traveled an average of 764 km (range, 10–2,575 km; 475 miles [range, 6–1,600 mi]) for care. There was no other history of IMO or metabolic bone disease in any of the families. All were sporadic cases. Gestation was uneventful for each of the children and without known exposures or risk factors.

We comprehensively reviewed the medical records to assess age of disease appearance, duration from first manifestations until diagnosis, upper extremity abnormalities, and family history. We reviewed the physical examinations reported by the treating physicians, surgeons, and hand therapists; one of us (C.A.G.) examined 5 of the 7 patients from our hospital. We confirmed and clarified the information available in the medical record with a direct discussion with 6 of the families.

We reviewed the serial upper extremity radiographs to assess the nature of disease progression. Clinical and radiographic data included the entire upper extremity, but we focused here on the hands, wrists, and elbows. Finally, we noted the treatment rendered for these patients, including hand therapy, medical (ie, medication), and surgical interventions. Five patients received bisphosphonate treatment in the attempt to block osteoclast-mediated bone destruction.[27] A detailed assessment of this medical approach to IMO is beyond the scope of this report.

RESULTS

Presentation

We noted the first manifestations of IMO to occur most commonly between 6 and 36 months of age (Table 1). Swelling and pain in the wrists and ankles were the first sign and symptom, respectively; in 5 patients, presentation included refusal to crawl using hands (2 patients) and pain with passive motion of the wrists and ankles (3 patients). Two other children first had difficulty ambulating, initially walking with a limp and subsequently refusing to walk. Five children had finger or thumb

FIGURE 1: Clinical characteristics of patients 2, 3, and 6. Note ulnar deviation, finger MCP joint extension, and thumb IP joint flexion.

interphalangeal (IP) joint contracture as an early difficulty; 1 was treated unsuccessfully with a trigger thumb release at age 5 years before being diagnosed with IMO.

Clinical manifestations

The most notable early problem was wrist pain; wrist swelling accompanied or shortly followed this presentation (Table 1). Loss of wrist motion and an ulnar deviation posture developed subsequently. Later findings, often years later, included deformities of the hands and elbows. The most common hand deformities were thumb IP joint flexion contracture (as noted above, this may be a primary presentation) and hyperextension of the metacarpophalangeal (MCP) joints. Most patients also lost elbow motion (especially extension) with deformity as a result of joint subluxation. Intermittent flares of pain and swelling in these affected joints were common. In general, 1 extremity was more severely affected than the other (no predilection for dominant extremity), although all patients were affected bilaterally (Fig. 1).

Diagnosis

Of the 8 patients, 7 were initially diagnosed with juvenile rheumatoid arthritis (JRA) despite an atypical presentation for JRA and a negative laboratory evaluation. A diagnosis of IMO was correctly made on first presentation in only 1 patient; she was the only patient not misdiagnosed with JRA. Several of the patients had an extensive multidisciplinary evaluation including chromosomal testing, magnetic resonance imaging of the head and neck, and nerve studies; all of these tests were negative. Juvenile rheumatoid arthritis treatments included nonsteroidal anti-inflammatory medication in all 7 patients, methotrexate in 6 patients, etanercept in 4 patients, and gold in 3 patients. None of these treatments was successful, although temporary improvements were reported, especially during the first 6 months with etanercept; thereafter, symptoms returned.

Idiopathic multicentric osteolysis was diagnosed at an average age of 4 years (range, 14 mo to 7.5 y) at the Center for Metabolic Bone Disease and Molecular Research by the constellation of clinical and radiographic findings. The interval between presentation and correct diagnosis averaged 30 months (range, 0 mo to 7 y) (Table 1).

Nephropathy was confirmed, and urinalysis demonstrated proteinuria in all of our patients. Proteinuria in IMO typically presents after osteolysis is visible radiographically and was helpful in confirming the diagnosis once IMO was considered a possibility.

Radiographic findings

Serial radiographs of the wrists and elbows were available for 6 patients, spanning an average 5.7-year span (range, 3–10 y).

Wrist and hand. The carpus was affected early, but this was often difficult to detect on initial radiographs, given that the carpus is primarily cartilaginous in early childhood. Notably, ossification of the capitate and hamate, typically apparent by age 1 year, did not occur in most patients. In 2 of our patients, the carpus initially ossified and gradually disappeared (by 7 y of age). Progressive resorption of the carpals led to an absent carpus with metacarpals resting on or near the distal radius in all patients. This occurred by age 3 years in the more severely affected patients, and by age 8 years in all.

Once osteolysis affected the carpus, 3 other findings were notable on radiographs. First, all patients had some degree of ulnar deviation of the hand. This was often asymmetrical, with the severely osteolytic wrist demonstrating earlier and more severe deviation. We noted this between ages 3 and 8 years. On final radiographs, the ulnar deviation averaged 40° (range, 10° to 60°). Second, the ulna became short relative to the radius in some patients (seemingly from lack of growth rather than osteolysis). This finding followed complete loss of the carpus and accompanied the ulnar deviation. The third finding was progressive loss of the proximal metacarpals, which typically presented at 8 years, with the earliest onset at age 5 years. Of 6 patients, 5 demonstrated metacarpal loss, but it varied from mild loss of only the proximal aspect to more severe involvement with loss of half the length of the metacarpals, typically showing a "sucked candy" appearance. The distal metacarpals were maintained in all patients (Fig. 2A, B).

Elbow. Radiographic abnormalities of the elbow became apparent only after changes were visible in the wrists. Initially, the radiographs were unremarkable, but

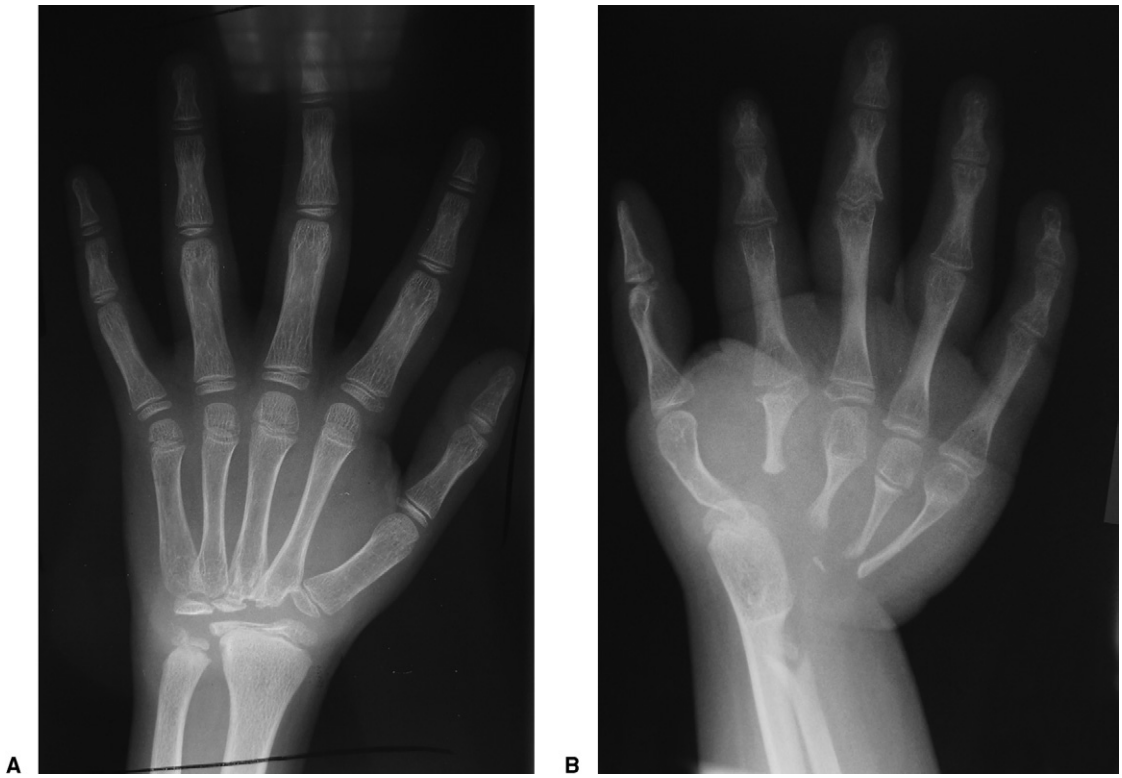

FIGURE 2: Mild and more severe appearance of the wrist on posteroanterior radiographs. **A** Unlisted patient; **B** patient 7.

they rapidly progressed after a first finding of nonspecific osteolysis. The next stage was flattening and widening of the greater sigmoid notch (proximal ulna articulating with the trochlea) with distal humerus articular surface flattening. Finally, at an average age of 7 years (range, 6–9 y), the elbows dislocated. Like the wrists, the elbow disturbances progressed at different rates (Fig. 3A, B).

Shoulder. The proximal humerus and glenohumeral joint were typically unaffected.

Supportive treatment

All patients received extensive occupational therapy. Given poor overall hand function and decreased strength, adaptive equipment and modification of activities of daily living were necessary. In addition, all patients received orthoses for the wrists and fingers, although with mixed results. Orthotic treatment did not appear to lead to improvement in joint positioning or joint motion. However, it did seem to help maintain surgical gains (see below).

Surgical intervention

Of the 8 patients, 5 were treated with upper extremity surgery (Table 1).

Patient 1 was treated at age 7 years, because of severe ulnar deviation deformity that limited function and caused pain. He underwent wrist joint release, extensor carpi ulnaris centralization, and temporary wrist joint pinning. His wrist alignment improved after surgery, although the initial correction was not maintained; by 2 years after surgery, his resting wrist posture and wrist motion were similar to before surgery. However, at latest follow-up at age 10 years, there was less pain in the operated wrist.

Patient 2 was treated at age 5 years with an open dorsal release and pinning of the middle, ring, and small MCP joints because of marked hyperextension. This was accompanied by closed manipulation and pinning of the distal interphalangeal joints of the middle and small fingers. An improvement in hand posture was noted (Table 2), and the patient's family considered the surgery helpful for function. However, there was a flare in pain after surgery, and the family has declined additional intervention.

Patient 3 was treated at age 5 years at another pediatric orthopedic hospital for hyperextension deformity of the MCP joints, limited motion of the IP joints, and flexed posture of the thumb IP joint. She underwent MCP joint capsulectomies and pinning in flexion with extensor tendon tenolysis and flexor pollicis longus tenotomy. Surgery and recovery were uneventful, and her family was pleased

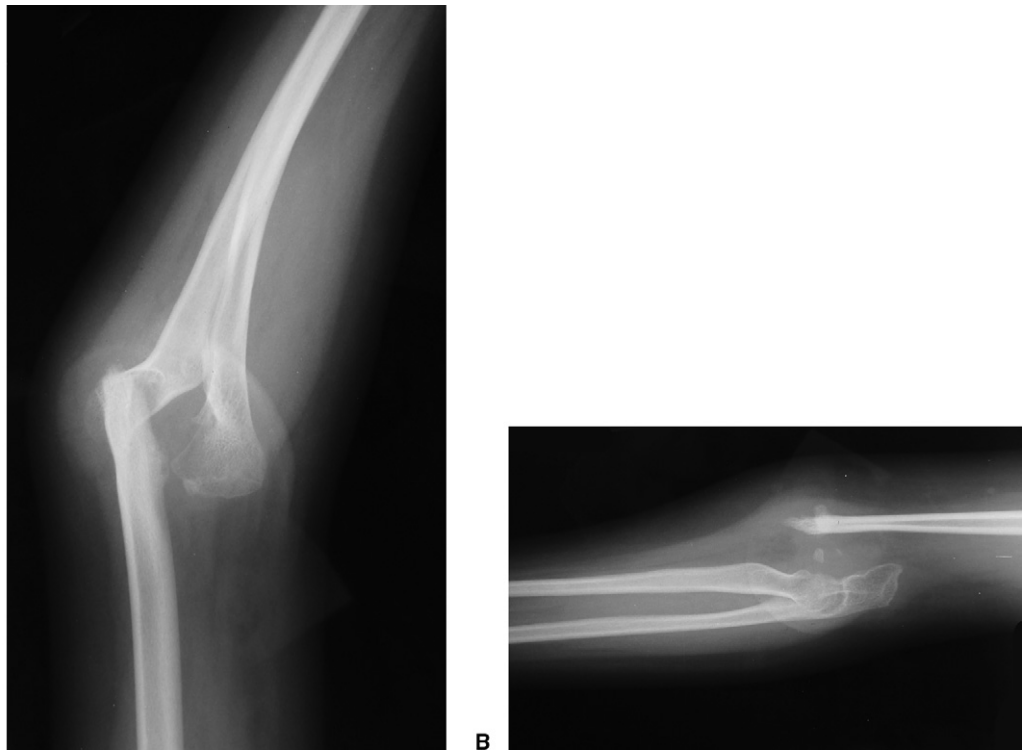

FIGURE 3: A Anteroposterior and **B** lateral radiographs of the elbow in patient 7. Note the pointed appearance of the distal humerus and flattening of the proximal ulna (greater sigmoid notch).

TABLE 2. Patient 2—Left Hand Range of Motion

Joint	Preoperative	2 y After Surgery
Middle finger		
MCP	+30/0	0/0
PIP	50/80	40/85
DIP	80/80	20/55
Ring finger		
MCP	+55/0	+5/+5
PIP	60/80	55/90
DIP	0/0	0/40
Small finger		
MCP	+60/0	+5/+5
PIP	55/80	80/90
DIP	55/55	15/30

+, hyperextension; PIP, proximal interphalangeal; DIP, distal interphalangeal.

with the hand position. A similar surgery is planned for the contralateral side (Table 3).

Patient 4 had a single surgery at age 25 years, a right wrist arthrodesis as the result of wrist pain and marked ulnar deviation. Although he had limited elbow motion bilaterally and some loss of wrist motion on the left, the right wrist was the patient's primary functional limitation. Before surgery, the wrist rested at 80° flexion with passive extension to a position of 20° flexion. The patient rested in 80° ulnar deviation and could not achieve a neutral posture. Accordingly, we successfully arthrodesed the wrist in a position of 5° flexion and neutral deviation; it improved but did not eliminate the pain.

Patient 5 had surgery in a staged fashion (right side at age 7 and then left side at age 8) with MCP joint capsulectomies and extensor tendon tenotomies with pinning for all of the fingers. Resting hand posture was improved and resulted in patient and family satisfaction.

DISCUSSION

The rarity of IMO has made the diagnosis challenging. Both IMO and JRA can present in the first 3 years of life with pain, stiffness, and joint-centered swelling. Given that JRA is a much more common and familiar diagnosis, an erroneous diagnosis of JRA is usually made in IMO. This is despite a negative laboratory evaluation (erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, etc) and atypical radiographs. Two factors are useful in clarifying the diagnosis of IMO. First, IMO presents with pain, swelling, and

TABLE 3. Patient 3—Right Wrist Range of Motion

	Right Side Preoperative	Right Side 10 mo After Surgery	Contralateral Left Side at Last Follow-up
Wrist (extension/flexion)	5/45	0/35	25/55
Wrist (radial/ulnar deviation)	45/55	60/70	50/60
Index finger			
MCP (extension/flexion)	0/0	0/0	+30/10
Long finger			
MCP (extension/flexion)	0/0	0/5	+25/+10
Ring finger			
MCP (extension/flexion)	+5/0	0/0	+30/+10
Small finger			
MCP (extension/flexion)	+15/0	+15/0	+90/+90
Thumb			
MCP (extension/flexion)	45/75	0/0	95° fixed flexion

Abbreviations as in Table 2.

stiffness in the wrists and ankles, whereas oligoarticular JRA commonly presents in the knee, and rheumatoid factor–negative JRA commonly presents in multiple joints. Second, the early carpal and tarsal osteolysis characteristic of IMO is infrequent in all types of JRA.[23]

The subsequent failure of JRA treatment leads to the search for another explanation.[23,28] As osteolysis becomes increasingly apparent, the diagnosis search is refocused on skeletal disease. We find that the earliest, most characteristic clinical features of IMO that assist in diagnosis include thumb IP joint fixed flexion posture together with pain and swelling in the wrists and ankles. Now, mutation analysis of MAFB will facilitate the diagnosis of IMO.[21]

The possibility of an early and correct diagnosis of IMO has been realized by the recent identification of missense mutations of MAFB, which is functionally important in osteoclast differentiation and activation in kidney development as well.[21] The identification of this genetic explanation for IMO opens new possibilities for treatment in the hopes of avoiding the crippling osteolysis.[21]

There are 3 groups of osteolytic bone disease, although notable variation exists within each.[29] Unicentric disease includes Gorham-Stout disease, which is bone loss in 1 location related to a disturbance involving lymphatic and vascular proliferation.[30] The second group is acro-osteolysis that includes scleroderma, psoriasis, Hajdu-Cheney syndrome, hyperparathyroidism, and other conditions with digital osteolysis. Finally, multicentric osteolysis is the most variable group, and may include individuals with nephropathy. Some of the patients in this group will have a genetic etiology.

Idiopathic multicentric osteolysis is 1 type of multicentric osteolysis (OMIM number 166300, AD). Torg-Winchester syndrome (OMIM number 259600) is another, different form that is transmitted as an autosomal recessive trait and primarily affects the hands and feet. An abnormality of matrix metalloproteinase-2 causes Torg-Winchester syndrome, which manifests as osteoporosis, subcutaneous nodules, and widening of the metacarpals or metatarsals.[31]

Idiopathic multicentric osteolysis has been reputed to be an autosomal dominant, autosomal recessive, or sporadic disorder. In fact, none of our IMO patients had affected relatives, and all had kidney disease of varying severity. They demonstrated a relatively consistent constellation of upper extremity features, including a thumb IP joint flexion contracture, MCP joint hyperextension of the other digits, wrist flexion and ulnar deviation, and decreased elbow motion. All had tarsal involvement of varying severity. Nonextremity manifestations have helped to achieve a correct diagnosis of IMO; the proteinuria of kidney disease is the most important and a hallmark finding with secondary common findings including frontal bossing, micrognathia, and hypertelorism.[23] On radiographs, carpal osteolysis with variable metacarpal resorption is the most characteristic finding. The elbow may also be involved, with dramatic bone resorption and loss of motion.

The role of surgical treatment for IMO remains un-

certain. Our experience suggests that the thumb IP joint flexion contracture can be addressed with an intramuscular lengthening of the flexor pollicis longus or, if unsuccessful, a tenotomy. The MCP joint hyperextension of the fingers can be improved with dorsal release, tenolysis or tenotomy, and temporary pinning. Wrist-based procedures, including joint release, tendon transfer, and pinning, often result in recurrent deformity but may provide pain relief. Wrist arthrodesis may also help symptoms, but bony union is unpredictable.[32] Previous reports of surgical intervention for severe osteolysis are few, have focused on unicentric disease such as Gorham-Stout disease, and have demonstrated mixed and often unsatisfactory results.[24]

The limitations of our study are those of a small, retrospective series involving a rare disease. The young age of our patients at the time of evaluation and treatment makes range of motion data and clinical assessment challenging. Yet, our experience with 8 patients includes a reasonable duration of follow-up with clinical and radiographic data.

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