Case Report

Dysplasia Epiphysealis Hemimelica

A Case Report with Novel Pathophysiologic Aspects

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Abstract Dysplasia epiphysealis hemimelica (DEH) is a rare developmental disorder. The underlying pathophysiology is largely unclear. Its diagnosis is based on clinical findings and may be difficult due to its low incidence and close relationship to other disorders such as osteochondroma. We describe a 13-year-old boy who presented with a unilateral lesion of the left medial femoral condyle and left ankle. In addition to standard diagnostic tools such as radiographs and MRI, arthroscopy-guided biopsy was performed; histologic/immunohistochemical findings from cartilage-bone specimens confirmed the diagnosis and provided novel information toward a disease mechanism. The cellular phenotype of clustered chondrocytes exhibited

characteristics of chondroprogenitor cells and terminally differentiated cells, suggesting dysregulation of resident progenitor cells. No other surgery was performed and during a 2 year period, we observed spontaneous ossification of the lesion associated with decreased joint impairment. Immunohistochemical analysis of the lesion provided a more accurate diagnosis and may contribute to unraveling potential novel mechanisms involved in its pathogenesis.

Introduction

DEH is a rare developmental disorder of the skeleton. It is characterized by asymmetric enlargement of the epiphyseal cartilage of long bones without involvement of other organs [22]. It commonly affects the lower extremity (tarsus, distal tibia, and distal femur) on one side of the body and often is restricted to either the medial or the lateral side of the limb (hemimelic) [20]. The medial joint compartment is affected twice as often as the lateral side. In approximately 2/3 of the cases, more than one epiphysis is affected [21]. DEH usually is diagnosed before the age of 15 years and males are affected as much as three times more often than females [22]. The reported incidence is approximately one in 1,000,000 [22]. It presents with three clinical scenarios: localized, affecting the hindfoot or the ankle only; classic, with a hemimelic distribution of the lower extremity; and generalized, involving the whole lower extremity from the pelvis to the foot [4].

Histologic/immunohistochemical findings include clumping of chondrocytes in a fibrillary chondroid matrix [5] and positive expression of Indian hedgehog/parathyroid hormone-like hormone (IHH/PTHrP), suggesting their participation in signaling pathways [5]. However, the pathophysiology of DEH remains unclear and gold

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Each author certifies that his or her institution has approved the reporting of this case report, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

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standards for diagnosis and therapeutic decision-making thus far are missing.

We describe a 13-year-old boy with DEH and a combined clinical, radiographic, and pathologic approach to diagnose DEH. Immunohistochemical findings suggested dysregulated resident progenitor cells as a potential disease mechanism in DEH.

Case Report

A 13-year-old boy first presented to our outpatient clinic with left knee and ankle pain of several months duration. The pain occurred primarily after sporting activities, particularly soccer, but not during prolonged rest. The patient had no relevant medical history. There was no history of trauma or overuse symptoms. Family history was negative for bone deformity, joint problems, or dysplasia. Standard laboratory blood parameters (blood count, coagulation, electrolytes, kidney function tests, liver function tests, and thyroid function tests) were all within normal range.

We observed asymmetric knock knees (left more than right) but no obvious gait disturbance. However, a massive Baker's cyst and major effusion of the left knee were evident. The patient had tenderness over the medial femoral condyle. Knee flexion and extension were accompanied by crepitation. The lateral aspect of the left knee was normal. A +15 mm limb-length discrepancy of the left lower extremity was present, as measured from the

anterior-superior iliac spine to the medial malleolus. The knee was stable, as determined by the Lachman test, anterior drawer test, posterior drawer test, pivot-shift test, and varus and valgus stress tests. A 5°-extension deficit of the left knee was noticeable with 120° flexion. We found reduced subtalar motion of the left hindfoot. Neurovascular examination of the left lower extremity was normal.

On the initial radiographs of the left knee, a prominent medial femoral condyle with loss of the curvilinear outline was evident (Fig. 1). In addition, irregularities at the bony-chondral interface of the medial more than of the lateral femoral condyle were visible. Inhomogeneous bony mineralization of the distal femoral epiphysis was detectable (Fig. 1). MRI of the left knee confirmed ossification disorders of both femoral condyles, medial more than lateral (Fig. 2). An irregularly shaped texture of the epiphyseal bone medially more than laterally was obvious. The cartilage of the medial epiphysis was distended (Fig. 2). Furthermore, at the mediodorsal femoral condyle, multiple associated bony structures representing accessory partially isolated and immature ossification centers were present. From the lateral part of the medial condyle, an abundant bony mass (3.5×1.5 cm) extended to the dorsal epiphysis resulting in a lateral shift of the structurally intact cruciate ligaments. In addition, the MRI showed signs of a medial meniscal tear corresponding to the medial knee pain. Conventional radiographs of both ankles also were taken. The right ankle appeared radiographically normal. On the left side, irregularities of the bony-chondral interface of the

Fig. 1A–B Initial (A) anteroposterior and (B) lateral radiographs of the left knee show a prominent medial femoral condyle with loss of curvilinear outline, accompanied by irregularities at the bony-chondral interface of the medial condyle more than the lateral femoral condyle. Inhomogeneous bony mineralization of the distal femoral epiphysis also was seen.

Fig. 2A–B T1-weighted (A) coronal and (B) sagittal MR images show an irregularly shaped texture of the epiphyseal bone medially more than laterally with immature ossification centers. The cartilage of the medial epiphysis was enlarged.

Fig. 3A–B (A) An anteroposterior radiograph of the left ankle shows irregularities of the bony-chondral interface of the medial talar shoulder including foci of inhomogeneous calcifications. (B) A T1-weighted coronal MR image of the left ankle confirms these findings and also shows a medial talocalcaneal coalition.

medial talar shoulder were evident (Fig. 3A). MRI of the left ankle confirmed small lesions with joint space enlargement and small foci of irregular calcification and showed typical signs for a talocalcaneal coalition (Fig. 3B), corresponding to the reduced subtalar motion. MRI of the pelvis showed no abnormalities.

To further evaluate the intraarticular cartilage impairment and suspected medial meniscal tear suggested by MRI, we performed arthroscopy of the left knee and biopsy of the medial femoral condyle. Arthroscopy showed considerable chondromalacia of the medial femoral condyle

(Fig. 4A, arrows). The cartilage of the femoral trochlea (Fig. 4B) showed similar irregularities as were seen in the medial condyle with multiple adherent cartilage fragments at the bony-chondral interface (arrows). Laterally, the cartilage appeared normal with no chondral defects as determined by probing with the hook instrument. The cruciate ligaments were shifted laterally as anticipated by MRI. From the dorsomedial aspect of the medial condyle, bone-cartilage cylinders (5 × 15 mm) were obtained outside the weightbearing zone, during arthroscopy of the left knee.

Biopsy tissue was fixed in 4% buffered formalin, rinsed with tap water, and decalcified in 10% EDTA solution at pH 7.4. From paraffin-embedded tissue, 2.5- μ m sections were cut and placed on glass slides pretreated with silane. Safranin O staining was performed according to the standard procedure [13]. For immunohistochemistry, deparaffinized

samples were pretreated according to antibody-specific protocols (see below) to improve immunoreactivity. The incubation with the primary antibody was performed overnight at 4°C. Binding of the secondary antibody to the primary was observed by the streptavidin-biotin method (LSAB kit; Dako, Hamburg, Germany). We used mouse

Fig. 4A–B Arthroscopy of the left knee showed (A) extensive chondromalacia of the medial femoral condyle (arrows) and (B) multiple adherent cartilage fragments at the bony-chondral interface of the trochlea (arrows).

Fig. 5A–L (A) Safranin O (Saf-O) staining showing a high proteoglycan content of cell clusters, (B) COMP staining of the pericellular matrix, (C) collagen Type I (Coll I) staining restricted to the pericellular matrix, (D) collagen Type II (Coll II) staining throughout the cartilage matrix, (E) PTHLP staining of the cells and the cartilage matrix, (F) collagen Type X (Coll X) staining which was mostly negative, (G) osteonectin/BM 40 (ON) staining of the pericellular matrix, (H) STRO-1 (a marker of human multipotent mesenchymal

stroma cells) staining of cells arranged in clusters, and (I) collagen Type II (Coll II) staining showing a gross streaky appearance, illustrate the histology and immunohistochemistry of osteochondral tissue in DEH. The osteochondral border contained an islet area in subchondral bone showing positive staining for (J) safranin O (Saf-O), (K) collagen Type I (Coll I), and (L) collagen Type II (Coll II) (Magnification, A–I, $\times 100$; J–L, $\times 25$).

Fig. 6A–B A comparison of T1-weighted transverse MR images of the left knee taken (A) at presentation and (B) at followup 12 months later shows no progression of the disease but rather progredient ossification of the lesions becoming confluent with the underlying epiphyseal bone.

monoclonal antibodies against collagen Types I and II (ACRIS, Hiddenhausen, Germany; pretreatment with pepsin), a mouse monoclonal antibody against collagen Type X (Quartett, Berlin, Germany; pretreatment with hyaluronidase followed by pepsin), a rabbit polyclonal antibody against COMP (provided by Frank Zaucke, Köln, Germany; pretreatment with hyaluronidase), a mouse monoclonal antibody against PTHLP (Calbiochem, Darmstadt, Germany; pretreatment in citrate buffer at 95°C), a mouse monoclonal antibody against PTH receptor Type I (Thermo Fisher Scientific, Inc, Fremont, CA; pretreatment in citrate buffer at 95°C), a rabbit polyclonal antibody against osteonectin/BM40 (provided by Ruppert Timpl, Martinsried, Germany; pretreatment with hyaluronidase), and a mouse monoclonal antibody against STRO-1 (R&D, Wiesbaden, Germany; pretreatment with hyaluronidase). Formalin-fixed paraffin-embedded sections of fetal growth plates were used as positive controls as described previously [13, 14]. A negative control as performed by omitting the primary antibody was performed to rule out unspecific staining.

The cartilage biopsy showed superficial irregularities with fibrillation resembling degenerative changes (Fig. 5). Overall cellularity was not markedly changed; however, the cells adjacent to bone tissue were arranged mostly in round or linear cell clusters (Fig. 5A–H). The cell clusters had a higher proteoglycan content compared with the interterritorial matrix as indicated by safranin O staining (Fig. 5A). The pericellular matrix showed intense staining for COMP and faint staining for collagen Type I (Fig. 5B–C). Collagen Type II showed homogeneous staining throughout the entire cartilage matrix (Fig. 5D). PTHLP was clearly expressed by the cells in DEH cartilage and also was detectable in the cartilage matrix (Fig. 5E). The PTH receptor Type I was expressed only weakly by single cells (data not shown) and collagen Type X was not

detected in the pericellular matrix of DEH cartilage (Fig. 5F). Osteonectin/BM40 was expressed most prominently in the pericellular matrix of cell clusters (Fig. 5G). Furthermore, the cells arranged in clusters adjacent to bone tissue were positive for STRO-1, a marker of human multipotent mesenchymal stroma cells (Fig. 5H). In the cartilage more distant from bone, we detected few STRO-1-positive cells. A faint fibrillary matrix [5] could not be detected; instead, there were some areas of gross streaky appearance most prominent in safranin O and collagen Type II staining (Fig. 5L). Another interesting observation was the presence of an islet area in subchondral bone exhibiting positive staining for safranin O and collagen Types I and II (Fig. 5I–K).

We recommended reducing soccer activities and other knee-stressing activities to provide some rest for the left knee. Sports with limited knee stress such as swimming (front crawl, backstroke) and cycling were recommended instead. Intermittent physical therapy was arranged. Followup was arranged in 6-month intervals. Owing to the recommended reduction of sport activity, the patient was pain free at last followup. MRI of the left knee 12 months later showed no progression of the disease, but rather progressive ossification of the former immature ossification centers and reduction in the size of the Baker's cyst (Fig. 6).

Discussion

DEH is a rare disorder in childhood and most commonly affects the epiphysis of long bones of the lower legs. Major joints such as the hip and spine rarely are involved [11, 17, 27]. DEH must be differentiated from other osteocartilaginous lesions such as synovial chondromatosis, capsular or paraarticular chondroma, and particularly solitary or

hereditary osteochondroma. Differential diagnoses also include myositis ossificans, infection, chronic infantile neurologic, cutaneous, and articular (CINCA) syndrome, tumoral calcinosis, and vascular or parasitic calcification [3, 16].

Conventional radiographs combined with MRI appear to be the diagnostic standard [4, 16]. MRI is particularly useful to display the exact location, extent of the lesion, and any joint involvement [19]. Findings also include epiphyseal osteochondroma-like lesions without metaphyseal changes arising from one side of the affected epiphysis. The irregular masses ossify early and enlarge the epiphysis when compared with the contralateral side [24]. This is particularly evident in the chronologic series of MR images presented here. Premature epiphyseal closure also may occur [22]. Computed tomography might provide additional information in defining the anatomic relations between the mass and bone in terms of cortical and medullar bone continuity [3, 15]. The benefit of an additional arthroscopy is controversial [3], but arthroscopy-guided biopsy, as performed in our patient, can support the clinical diagnosis [27].

The pathobiologic mechanisms of cartilaginous overgrowth in DEH have not been identified yet [23] and might include blood flow abnormalities of the fetal epiphysis and loss of polarity of the epiphyseal cartilage cells [22]. In addition, the lesions of DEH histologically resemble secondary ossification centers [10, 18]. In our patient, followup MRI showed progressive ossification of the lesions. Furthermore, it has been suggested DEH results from failure of peripheral epiphyseal cartilage [10].

Histologically, there are similarities between DEH and osteochondromas, which represent the most common benign bone tumors and commonly arise in association with a mutation of the EXT gene family [5]. Morphologic results in our case embraced the absence of the classic growth plate architecture and clustering of chondrocytes, although arranged more longitudinally than described elsewhere [5]. In addition, a faint fibrillary matrix around these chondrocyte clusters as described [5] generally was absent, although distinct areas of inhomogeneous streaky staining pattern for collagen Type II, COMP, and safranin O were clearly present. We also noted an islet consisting of fibrocartilaginous tissue (rich in proteoglycans and positive for collagen Types I and II) localized in the subchondral bone. This could be interpreted as local failure of chondrocyte differentiation and subsequent replacement by bone tissue or as part of a cartilage band surrounded by cancellous bone as described by Glick et al. [10]. In line with a previous report, PTHLH was expressed abundantly on a protein level in our specimen [5]. This might be of particular pathogenetic interest because, in hereditary multiple osteochondromas, PTHLH

expression reportedly is downregulated as a consequence of underlying mutations in EXT genes that are involved in heparan sulfate biosynthesis [6]. In another publication, however, PTHLH was expressed in osteochondromas from females and adolescent males, suggesting age- and gender-dependent influences [12]. Moreover, upregulation of PTHLH expression also may be observed in the progression of osteochondroma to peripheral chondrosarcoma [6]. In the absence of histopathologic signs of malignancy, the prominent expression of PTHLH therefore is consistent with the notion that mutations in EXT genes may not be a causal factor in DEH as hypothesized by other investigators [5]. Unlike the majority of cases described by Bovee et al. [5], we could not find relevant expression of the PTH receptor Type I. Another, very early, pathogenetic hypothesis postulated the failure of hypertrophic chondrocytes to undergo apoptosis resulting in prolonged persistence of these cells [26]. We therefore performed immunostaining for collagen Type X, a marker of hypertrophic chondrocytes. Its negative pericellular staining is in accordance with the cellular morphology that does not include a marked increase in cell size. In contrast, osteonectin/BM40, which has been described in the hypertrophic zone of the growth plate [1], was actively expressed in DEH cartilage. Most interestingly, we found STRO-1, a marker of multipotent mesenchymal stroma cells, was expressed in most cells from DEH cartilage. It is not known whether osteochondroma tissue contains STRO-1-positive cells, but it has been reported that 2% to 10% of cells isolated from chondrosarcoma tissue are STRO-1-positive [9]. We and others also have identified small subpopulations of multipotent mesenchymal progenitor cells in human articular cartilage [2, 7, 8, 25]. The immunohistochemical results derived from DEH cartilage are suggestive for a defect leading to accumulation of cells comprising certain characteristics of chondroprogenitor and terminally differentiated cells.

As in our case, patients might be managed without major surgery and on ossification of the lesion, relief of symptoms may be experienced. Our morphologic data provide novel findings regarding the pathogenesis of DEH, which might involve a defect in keeping resident progenitor cells in a quiescent stage that leads to accumulation of cell clusters with a phenotype combining characteristics of chondroprogenitor cells and growth plate chondrocytes. This may be related to the natural course that usually is characterized by subsequent ossification of lesion sites. Therefore, the stages of the disease and possible secondary changes should be kept in mind when comparing results of different patients. Additional studies are warranted to reveal the underlying pathomechanism of DEH in view of future therapeutic remedies.

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