Dysplasia epiphysealis hemimelica: a histological comparative study with osteochondromas

J. Stevens
T. J. M. Welting
A. M. Witlox
L. W. van Rhijn
H. M. Staal

Abstract

Purpose Dysplasia epiphysealis hemimelica (DEH) is a rare developmental disorder resulting in epiphyseal overgrowth. Based on histological appearance, it is often described as an osteochondroma or osteochondroma-like lesion, although clinical differences exist between DEH and osteochondromas. The aim of this study was to test whether DEH and osteochondromas are histologically identical diseases.

Methods Tissue samples of two age- and gender-matched cases with DEH and hereditary multiple exostoses were histologically compared. Sections were stained with Safranin-O for detection of proteoglycans and immunohistochemistry was performed for detection of collagen type II, collagen type X as a marker of hypertrophic chondrocytes and Sox9 as a marker of proliferative chondrocytes. Due to the rarity, descriptions of the included DEH patients were outlined.

Results Histologically, chondrocyte clusters in a fibrillary matrix, a thick disorganised cartilage cap and ossification centres with small amounts of unabsorbed cartilage, were observed in DEH. In contrast, cartilage organisation of osteochondromas displays characteristics of the normal growth plate. Collagen type II was clearly detected in the cartilaginous extracellular matrix in osteochondromas, while weak expression was observed in DEH. Collagen type X was not detected in DEH, while expressed in the matrix surrounding hypertrophic chondrocytes in osteochondromas. Sox9 staining was positive in hypertrophic chondrocytes in osteochondromas, while expressed in nuclei of chondrocyte clusters in DEH.

Conclusion Both morphological and immunohistological differences were observed in histological sections of DEH

and osteochondromas. These results support the previously identified clinical, radiological and genetic differences and imply a different aetiology between DEH and osteochondroma formation.

Introduction

Dysplasia epiphysealis hemimelica (DEH), or Trevor's disease, is a rare developmental disorder characterised by asymmetric overgrowth of the epiphyseal cartilage of long bones.[1-3] It is usually restricted to one side of the epiphysis, with the medial side affected twice as often compared with the lateral side. The ankle and wrist are the most affected joints for the lower and upper extremities, respectively, while involvement of multiple joints is common.[4] DEH is usually diagnosed in children aged between two and eight years and is three times more often diagnosed in boys.[4,5] Most reported complaints at first presentation are pain, limitation in range of motion, and deformity or swelling of the affected joint. Conventional radiography commonly results in diagnosing DEH, while CT and MRI are useful in the preoperative planning.[6] Treatment of symptomatic lesions consists of surgical resection of the lesion, although an expectative policy with follow-up is justifiable in asymptomatic lesions, since malignant transformation has never been reported.[7]

Histopathologically, DEH is a tumorous disease characterised by osteocartilaginous overgrowth of the epiphysis and is often described as an epiphyseal osteochondroma or as an osteochondroma-like lesion. This description suggests a common aetiology between DEH and osteochondromas. However, osteochondromas are far more common benign tumours with an incidence of 1:50 000, while DEH is extremely rare with a reported incidence of 1:1 000 000.[8,9] Next to the difference in incidence, there are differences in appearance of the cartilaginous overgrowth. Osteochondromas are cartilage capped bony

Department of Orthopaedic Surgery, Research School CAPHRI, Maastricht University Medical Centre, Maastricht, The Netherlands

Correspondence should be sent to: Dr H. M. Staal, Department of Orthopaedic Surgery, Maastricht University Medical Centre+ P. Debyelaan 25, P.O. Box 5800, 6202AZ Maastricht, The Netherlands.
E-mail: h.staal@mumc.nl

projections of the metaphysis of a bone, while DEH arises from the epiphysis. As a result, DEH and osteochondromas were seen as different entities based on location of appearance, while 10% to 15% of osteochondroma patients present with multiple osteochondromas, caused by the autosomal dominant disorder hereditary multiple exostoses (HME).[10-12] Bovee et al showed that exostosin (EXT) genes are not involved in the pathogenesis in DEH, while those genes were mutated in 90% of all HME patients, suggesting a difference in aetiology between both diseases.[7] Despite those differences, DEH is still described as an osteochondroma-like lesion in literature based on histopathological appearance.[13-21] The aim of this study was to morphologically and immunohistochemically compare DEH with HME, in order to investigate if these diseases are histologically identical. Therefore, we will report histological sections of two patients with DEH and compare them with sections of two age- and gender-matched patients with multiple osteochondromas caused by HME. In addition, brief descriptions of the included cases with DEH will be given due to the rarity of DEH.

Patients and methods

Two patients with a histopathologically confirmed diagnosis of DEH were identified from the patient files of the Department of Orthopaedics of the Maastricht University Medical Centre. Both participants underwent surgery for symptomatic DEH. These patients were compared with two age- and gender-matched patients diagnosed with HME. Patient charts were reviewed for acquiring the case descriptions.

Tissue sampling and processing

Tissue was available for all included patients at the start of this study. The local ethics committee approved the use of this tissue for this study. Verbal informed consent was obtained from all patients and/or their parents. All specimens were fixed in 4% buffered formalin for at least 72 hours. After rinsing with tap water, tissues were decalcified with 10% EDTA solution for up to six weeks. Sections of 5 μm were cut from paraffin-embedded tissue and placed on glass slides.

Histological evaluation

After deparaffinisation and rehydration, sections were treated with hyaluronidase for 30 minutes at 37°C or boiled in citrate buffer for 30 minutes, according to the antibody-specific regimens to improve immunoreactivity (Table 1). Endogenous peroxidase activity was blocked and sections were rinsed with phosphate-buffered saline. Subsequently, sections were incubated with the primary antibody for staining of collagen type II, collagen type X and Sox9. Details of the antibodies and negative controls are shown in Table 1. Samples were incubated with an anti-mouse secondary antibody conjugated with Horseradish Peroxidase (Dako, Glostrup, Denmark). Adding of diaminobenzidine solution resulted in visualisations of the antigens of interest. Haematoxylin was used for counterstaining of the sections.

In addition, a routine haematoxylin and eosin (H&E) staining and Safranin-O staining were performed as described before.[22] Sections were analysed and digitised by light microscopy (Axioscope A1, AxioVision LE release 4.8.2, Carl Zeiss, Germany).

Results

Case descriptions

In order to compare DEH and osteochondromas, two age- and gender-matched patients with HME were included. Because of the rarity of DEH, a brief description of these patients will be given and clinical data of the included cases is reported in Table 2.

Case 1: dysplasia epiphysealis hemimelica

An eight-year-old boy visited our outpatient clinic with pain and swelling of his left ankle. The pain progressed over several months, resulting in sparing of the ankle during normal daily activities. History was negative for trauma or overuse. Family history was positive for Scheuermann's disease.

Physical examination showed an antalgic gait with sparing of the left ankle. Inspection revealed an anteriorly located swelling of the left talocrural joint. Passive dorsiflexion of the ankle was restricted to 0° and resulted in pain. The boy experienced tenderness over the left musculus extensor hallucis longus tendon. The range of motion

Table 1. Details of used antibodies and protocol.

Antigen	Manufacturer	Antigen retrieval	Antibody incubation time	Dilution	Secondary antibody	Negative control
Collagen II monoclonal (II6B3)	Developmental studies Hybridoma Bank	Hyaluronidase (4 mg/mL), 30 min at 37°C	1 h at room temperature	1:200	Dako Envision HRP mouse	Monoclonal IgG1 (Dako, Glostrup, Denmark)
Collagen X monoclonal (X53)	Quartett	Hyaluronidase (4 mg/mL), 30 min at 37°C	Overnight at 4°C	1:25	Dako Envision HRP mouse	Monoclonal IgG1(Dako, Glostrup, Denmark)
Sox 9 monoclonal (sc-166505)	Santa Cruz Biotechnology Inc.	Citrate buffer, boiled, 30 min	Overnight at 4°C	1:50	Dako Envision HRP mouse	Monoclonal IgG2 (Dako, Glostrup, Denmark)

HRP, horseradish peroxidase

Table 2. Clinical data of patients with DEH and HME.

Disease	Age (yrs)/ sex	Clinical data	Location	Radiology
DEH Case 1	9/ Male	• Progressive pain • Swelling of the left ankle	Left distal tibia	• Overgrowth of the epiphysis • Joint space narrowing between tibia and talus • Two posteriorly located centres of ossification
HME Case 1	8/ Male	• Limitation during daily activities • Aesthetic burden • Positive family history for HMO	Left distal femur*	• Scapula inferior,[†] proximal humeri,[†] distal radius,[†] distal ulna,[†] proximal femur,[†] left SI-joint,[‡] left acetabulum rim,[‡] 3th and 4th rib right,[‡] left distal femur
DEH Case 2	3/ Male	• Progressive pain left knee • Palpable swelling lateral knee joint	Left distal femur and proximal tibia	• Overgrowth and ossifications in epiphysis of the distal femur and proximal tibia
HME Case 2	3/ Male	• Progressive painless deformity left forearm • Positive family history for HMO	The left distal ulna*	• Proximal humeri,[†] distal femur,[†] proximal fibula,[†] distal fibula,[†] right scapula,[‡] left proximal tibia[‡] and left distal ulna[‡]

DEH, dysplasia epiphysealis hemimelica; HME, hereditary multiple exostoses

* Location of resected material used for further histological evaluation

[†] Bilateral occurrence of osteochondromas

[‡] Unilateral occurrence of osteochondroma

of the left knee and left hip was unlimited and there was no leg length discrepancy.

Radiographs showed overgrowth of the medial epiphysis of the distal tibia, resulting in joint space narrowing between the distal tibia and talus. Furthermore, sclerosis of the talus and distal epiphysis of the tibia and two posteriorly located centres of ossification were visible in the lateral radiograph (Fig. 1a, white arrows). MRI confirmed overgrowth of the distal tibial epiphysis and showed tibiotalar articular incongruence. High signal intensity was observed in the bony overgrowth (Fig. 1b, white arrow). In addition, thickening of the articular cartilage of the left talocrural joint was visible.

During surgery, both the cartilage capped bony protuberance of the anterior distal tibia and the posteriorly located ossification centres were resected (Fig. 1c, white arrows). Intra-operative physical examination showed a maximum ankle dorsiflexion angle of 15°.

Case 2: dysplasia epiphysealis hemimelica

The second case was a three-year-old boy, who visited our outpatient clinic with left knee pain. The pain progressed over several months, resulting in an antalgic gait and a painful left hip. There was no history of trauma or overuse. Family history was negative for bone deformations, joint problems or dysplasia.

No abnormalities were observed during inspection. A gait disturbance was present, with the patient keeping his left knee straight during the entire gait cycle. There was a full range of motion of the left knee, although flexion of the knee provoked pain. An evident swelling was palpated at the lateral side of the left knee joint. The patient did not tolerate further physical examination of his left knee, due to the experienced amount of pain.

Two calcified regions were visible in the lateral region of the cartilaginous epiphysis of both the distal femoral and proximal tibia of the left knee in the conventional radiographs (Fig. 2a, white arrows). An MRI scan confirmed
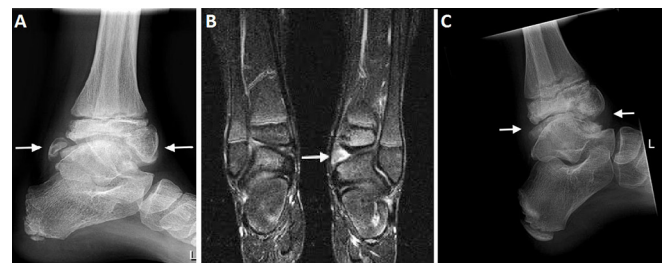

Fig. 1 (**a**) Pre-operative lateral conventional radiograph of the left ankle. (**b**) Pre-operative coronal STIR MRI scan (TR 2000/ TE 55) of both ankles. (**c**) Post-operative lateral conventional radiograph of the left ankle.
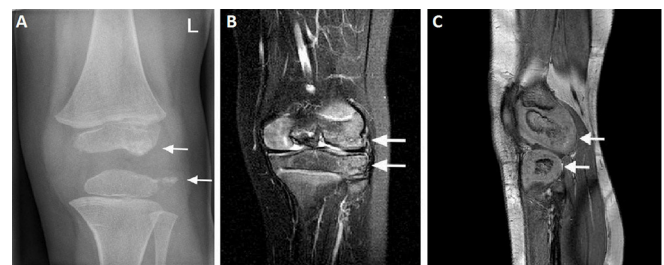

Fig. 2 (**a**) Pre-operative anteroposterior radiograph of the left knee. (**b**) Pre-operative coronal T2-weighted MRI scan (TR/TE 2968/70 ms). (**c**) Pre-operative sagittal balanced fast field echo (bFFE) MRI scan (TR/TE 17/4).

these observations and showed epiphyseal overgrowth (Fig. 2b and 2c, white arrows).

The cartilage overgrowth of the lateral femoral epicondyle of the left knee was resected during surgery. Cartilaginous thickening of the tibial plateau was observed intra-operatively, but was not resected by the surgeons.

Histological evaluation

Haematoxylin and eosin

H&E staining showed the characteristic lobulated cartilage caps in osteochondromas (Fig. 3a and 3c). Characteristics

of the growth plate architecture were detected, with chondrocytes orientated in columns expressing a different stage of maturation; resting chondrocytes (Fig. 3e, grey arrow), proliferating chondrocytes (Fig. 3e, white arrow) and hypertrophic chondrocytes (Fig. 3e, black arrow) were all identified. In contrast, the cartilage of DEH was less organised and showed clusters of chondrocytes (Fig. 3d and 3f, black arrows). Chondrocytes had a relatively smaller cell volume as compared with chondrocytes in osteochondromas (Fig. 3b and 3d). In addition, ossification centres (Fig. 3b and 3d, white arrows) and small amounts of unabsorbed calcified cartilage were observed in the cartilage cap in DEH (Fig. 3b and 3d, grey arrows).

Safranin-O

Sections were stained with Safranin-O for detection of proteoglycans in the cartilage cap. Staining was positive in both osteochondroma and DEH (Fig. 4a and 4b). As in the H&E staining, characteristics of the growth plate architecture were detected in osteochondromas, with proliferative chondrocytes (Fig. 4a, white arrow) beneath the perichondrium and hypertrophic chondrocytes (Fig. 4a, black arrow) above the zone of ossification. In contrast, chondrocytes were arranged in disorganised cell clusters with a high density of chondrocytes in DEH (Fig. 4b, white arrows).
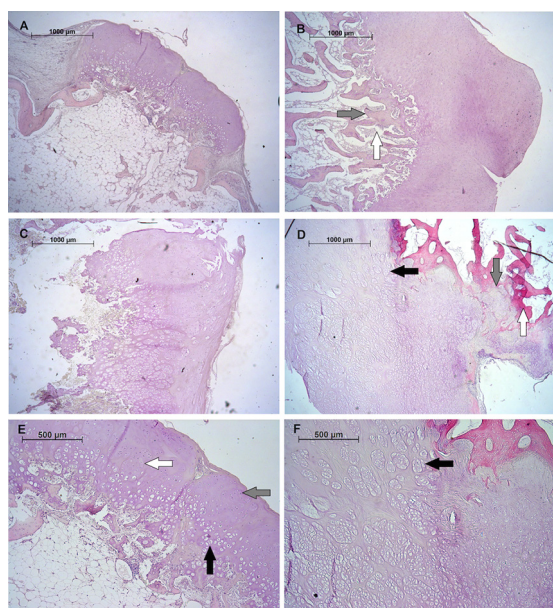

Fig. 3 (a, c) Haematoxylin and Eosin (H&E staining in osteochondroma in cases I and II, respectively (2.5×). **(b, d)** H&E staining in DEH in cases I and II, respectively (2.5×). Clusters of chondrocytes (black arrow), ossification centres (white arrows) and small amounts of unabsorbed calcified cartilage (grey arrows) were detected. **(e)** H&E staining for osteochondroma case I (5×), hypertrophic chondrocytes (black arrow), proliferative chondrocytes (white arrow) and resting chondrocytes (grey arrow) were identified. **(f)** H&E staining for DEH case I (5×), clusters of chondrocytes were detected (black arrow).

Collagen type II

Both osteochondromas and DEH showed clear expression for collagen type II (Fig. 4c-f). Most intense staining was observed in the extracellular matrix surrounding proliferating and hypertrophic chondrocytes in osteochondromas (Fig. 4c and 4e, black arrows), with faint expression in the resting zone (Fig. 4c, white arrow). In DEH, homogenous faint expression of collagen type II was clearly seen in the extracellular matrix surrounding clusters of chondrocytes (Fig. 4f, white arrows), with increased expression beneath the perichondrium (Fig. 4d, white arrow). No signal was detected in negative controls (Fig. 4g).

Collagen type X

Sections were stained with an anti-collagen type X antibody to determine the presence of hypertrophic chondrocytes. Expression of collagen type X was observed in the extracellular matrix directly surrounding hypertrophic chondrocytes in osteochondromas (Fig. 5a, white arrow), while it was not observed in other zones of the cartilage cap (not shown). Collagen type X expression was not detected in DEH (Fig. 5b). No expression was detected in the negative control (Fig. 5c).

Sox9

Expression of Sox9, normally detected in proliferative chondrocytes, was observed in both osteochondromas and DEH (Fig. 5d-g). The nuclei of almost all hypertrophic chondrocytes in osteochondromas in the vicinity of the chondro-osseous junction stained positive (Fig. 5d and 5f, white arrows). Only a few proliferative chondrocytes showed expression for Sox9 (Fig. 5f, black arrow). Nuclear expression of Sox9 was detected in chondrocytes in the entire cartilage cap in DEH (Fig. 5e, white arrows). The clusters of chondrocytes in DEH also showed nuclear Sox9 expression (Fig. 5g, white arrow). In addition, large areas of unabsorbed calcified cartilage beneath the cartilage cap were observed in osteochondromas (Fig. 5d, black arrows), which were not detected in DEH. No signal was observed in negative controls (Fig. 5h).

Discussion

In this study, we described two cases of the extreme rare disease DEH and histologically compared this disease with more common osteochondromas in HME, since lesions in both diseases are often stated as histologically identical.[13-21] The aim of this study was to histologically compare DEH and osteochondromas and investigate whether both diseases are histologically identical diseases.

Instead of finding similarities, some major (immuno) histological differences between DEH and osteochondromas
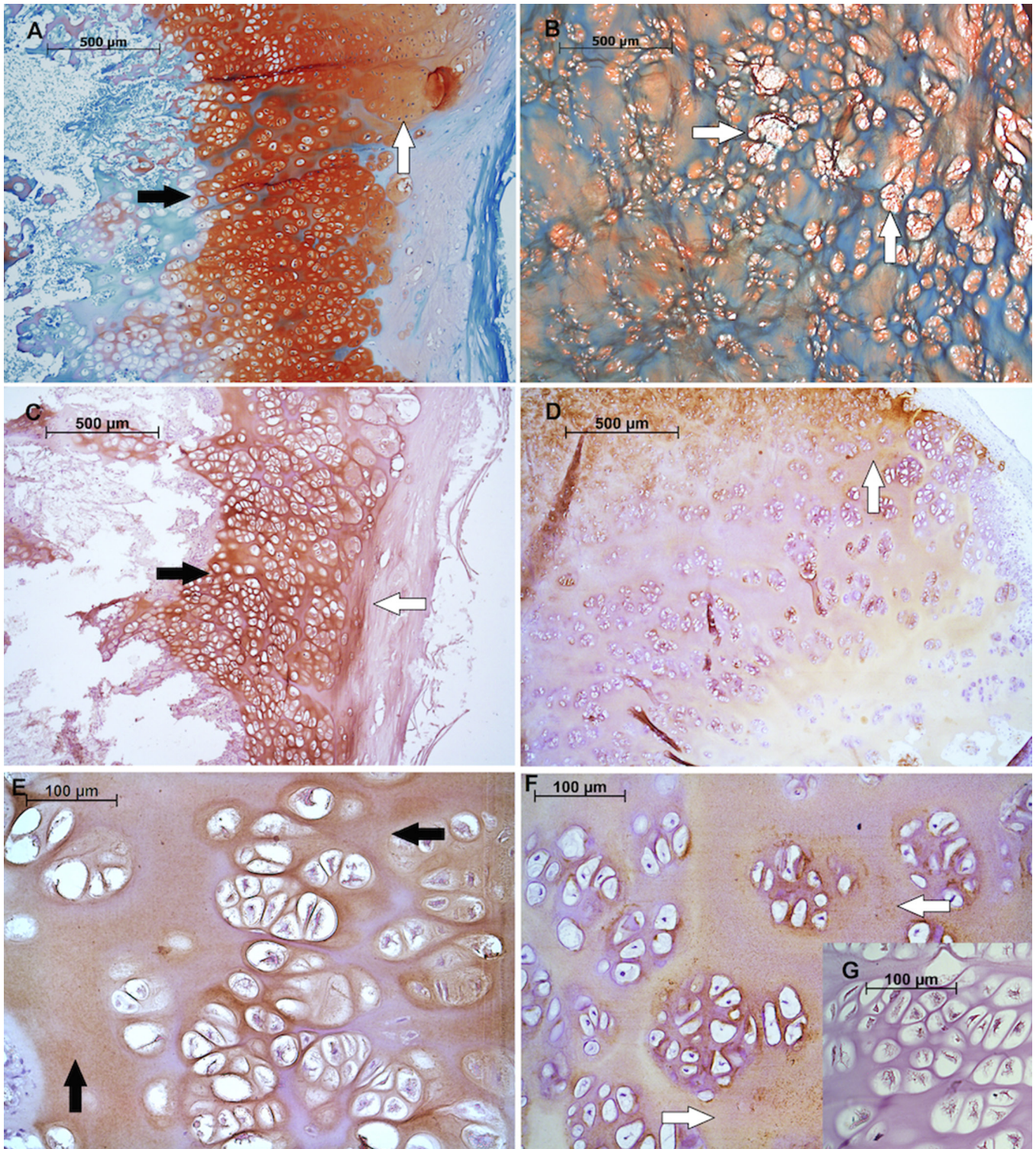
Fig. 4 (**a**) Positive Safranin-O staining in osteochondroma (5×). Hypertrophic chondrocytes (black arrow) and proliferative chondrocytes (white arrow) were detected. (**b**) Safranin-O staining in DEH (5×) showed disorganised cell clusters (white arrows). (**c**) Collagen type II staining in osteochondroma (5×), with high expression in the extracellular matrix surrounding hypertrophic chondrocytes (black arrow) and faint expression in the resting zone (white arrow). (**d**) Collagen type II staining in DEH (5×). Faint expression was observed, with increased expression beneath the perichondrium (white arrow). (**e**) Collagen type II staining in osteochondroma (20×), with high expression in the extracellular matrix surrounding hypertrophic chondrocytes (black arrow). (**f**) Collagen type II staining in DEH (20×). Faint expression was detected in the extracellular matrix surrounding clusters of chondrocytes (white arrows). (**g**) Negative control for collagen type II (20×).
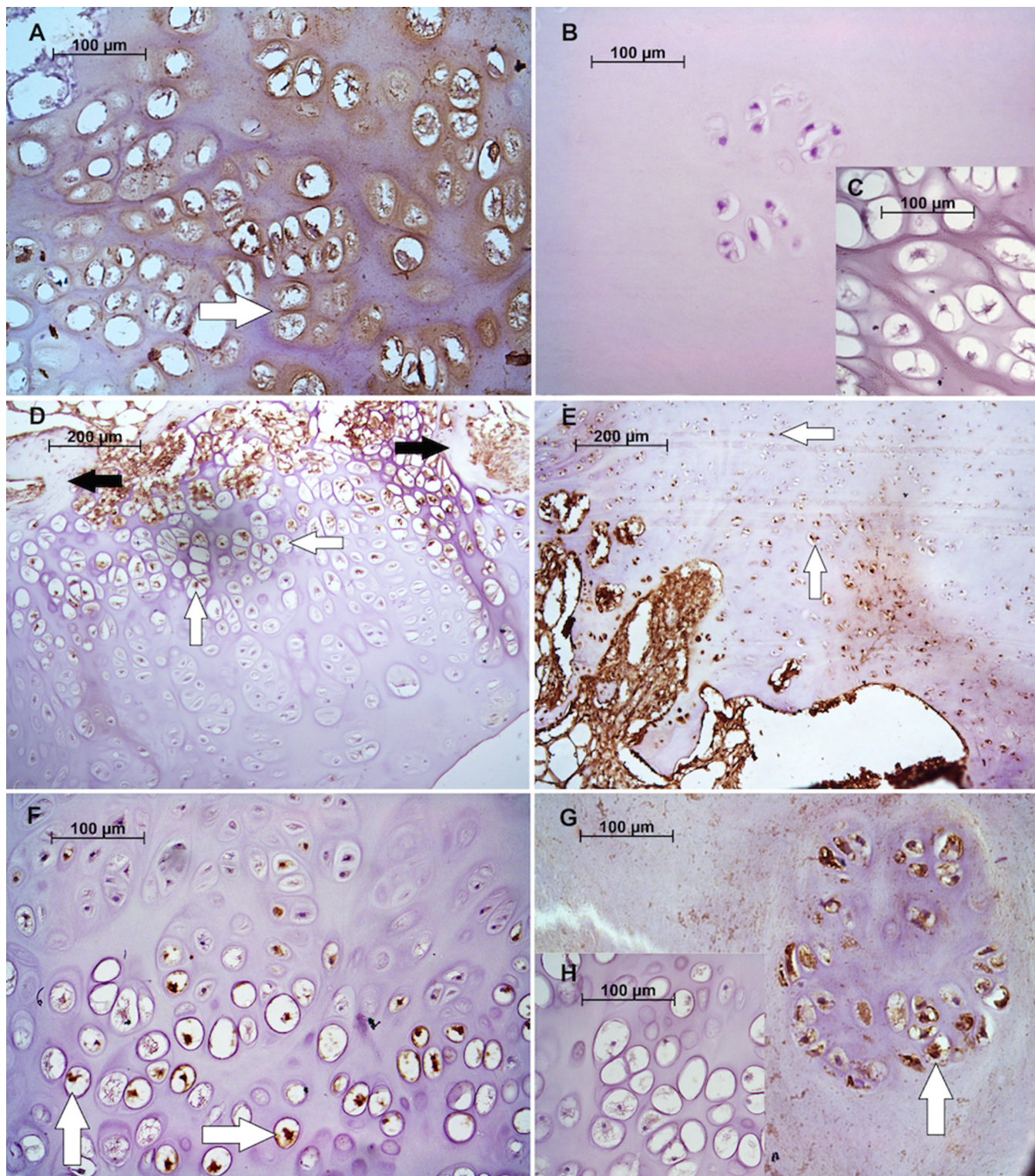
Fig. 5 (**a**) Collagen type X staining in osteochondroma (20×). Positive staining was detected in the extracellular matrix surrounding hypertrophic chondrocytes (white arrow). (**b**) Collagen type X staining in DEH (20×). (**c**) Negative control for collagen type X (20×). (**d**) Sox9 staining in osteochondroma (10×) showed nuclear expression in hypertrophic chondrocytes (white arrows). Large amounts of unabsorbed calcified cartilage were detected (black arrows). (**e**) Sox9 staining in DEH (10×). Nuclear expression was detected in chondroyctes in the entire cartilage cap (white arrows). (**f**) Sox9 staining in osteochondroma (20×), showed nuclear expression in hypertrophic chondrocytes (white arrows) and proliferative chondroyctes (black arrow). (**g**) Sox9 staining in DEH (20×). High expression was detected in the nuclei of chondrocyte clusters (white arrow). (**h**) Negative control for Sox9.

were observed. Osteochondromas showed a lobulated cartilaginous architecture with characteristics of the growth plate, i.e. different zones of maturations of chondrocytes. Compared with a normal growth plate, chondrocytes were less well aligned in columns in osteochondromas although this was known from previously reported studies of osteochondromas.[12,23-26] This partial growth plate structure was absent in the cartilage cap in DEH, where a thick, disorganised cartilage cap was observed.

Previous studies showed some characteristic morphological features of cartilage in DEH. These characteristics were clusters of chondrocytes surrounded by a faint fibrillary matrix,[7] and ossification centres in the cartilaginous matrix with a small area of unabsorbed calcified cartilage above it.[23,24,27,28] We identified these clusters of chondrocytes and ossification centres in both cases of DEH. The faint fibrillary matrix surrounding these clumps of chondrocytes was also clearly detected in the Safranin-O and collagen type II staining. In addition, only small areas of unabsorbed calcified cartilage were detected above the centres of ossification in DEH. Therefore, our observations in DEH were consistent with literature and show some significant morphological differences with osteochondromas.

Some additional immunohistological differences between both diseases were presented as well. In line with a previous study of Perl et al, clear staining of collagen type II in the cartilage matrix surrounding the clumps of chondrocytes was detected.[28] Collagen type II staining differed in osteochondromas, where the most obvious staining was detected in the extracellular matrix between the proliferating and hypertrophic chondrocytes, as expected based on a previous study in osteochondromas.[25] This finding additionally suggests a difference in tissue characteristics between both diseases.

The performed immunostaining for collagen type X, a marker of hypertrophic chondrocytes, did not show collagen type X in DEH. Besides, no cells with the cellular morphological hypertrophic appearance were identified in DEH. The results of this study, together with the results of Perl et al, who were also not able to identify collagen type X and hypertrophic chondrocytes in DEH,[28] refute Trevor's hypothesis. Trevor hypothesised that DEH results from failure of hypertrophic chondrocytes to undergo apoptosis and therefore persist.[2] In contrast to DEH, collagen type X was detected in the pericellular matrix between hypertrophic chondrocytes in osteochondromas as expected.[25,26,29] This difference in collagen type X expression also suggests that both diseases are not identical.

A defect in keeping resident progenitor cells in a quiescent stage is a newer hypothesis regarding the potential pathogenesis of DEH. This would result in accumulation of cell clusters and chondrocytes with phenotypic characteristics of chondroprogenitor as well

as growth plate-like cells.[28] As a result, chondrocytes should be able to proliferate and express proliferative markers. Expression of the chondrogenic transcription factor Sox9, which is expressed in proliferative chondrocytes in normal growth plates, was therefore evaluated. Clear expression of Sox9 was observed in the nuclei of the chondrocytes arranged in clusters in DEH. These results may therefore support this newer hypothesis of the pathogenesis of DEH.

In addition, an unexpected result was observed in the Sox9 staining. Differences in expression patterns of Sox9 were detected between DEH and osteochondroma, since Sox9 was expressed in some proliferative chondrocytes and almost all hypertrophic chondrocytes in osteochondromas. Since Sox9 is a proliferative marker, staining was expected in proliferative instead of hypertrophic chondrocytes. However, previous histological studies in osteochondromas also reported positive staining of proliferative markers in hypertrophic chondrocytes instead of proliferative chondrocytes.[29] It was suggested that osteochondroma chondrocytes presents some characteristics of hypertrophic cells (i.e. expression of collagen type X), but these cells are even capable to proliferate and fail to terminally differentiate.[29] Our results match with this suggestion, since hypertrophic chondrocytes were observed expressing both collagen type X and Sox9 in osteochondromas. However, the difference in expression of Sox9 in DEH and osteochondromas further strengthens the evidence that DEH and osteochondromas were (immuno) histologically not identical.

Thus, DEH and osteochondromas seem not identical diseases based on both the morphological and immunohistological evaluation of sections of patients with DEH and osteochondromas in this study. Furthermore, there are more differences between both diseases that imply a different aetiology. Both diseases appear at a different location and at a different age, with DEH arising from epiphyses of (young) children aged between two and eight years.[4] In contrast, osteochondromas arise from the metaphysis of long bones and generally affect older children. Osteochondromas increase in size in the first and second decades of life and cease to grow when the growth plates close.[11] Next, EXT-related pathways are involved in the pathogenesis of osteochondromas, while these genes were not involved in the pathogenesis of DEH, as shown by Bovee et al.[7] Besides, there is no evidence for genetic inheritance of DEH while mutated EXT genes were inherited in an autosomal dominant way in HME.[7,11,12,23] Finally, malignant transformation of osteochondromas to secondary peripheral chondrosarcoma is observed in 0.5% to 5% of the patients with osteochondromas, while malignant transformation of DEH has not been reported before.[11,12]

In conclusion, in this study two cases of DEH were described and histologically compared with age- and gender-matched patients with osteochondromas. In contrast to previous literature, major morphological and immunohistological differences were detected between both diseases. Therefore, we concluded that two diseases who genetically and clinically differ also show major differences in terms of morphology and immunohistochemistry. These results together strongly suggest that DEH has a different aetiology than osteochondromas. Additional studies are necessary to further elucidate the exact differences in pathogenesis between DEH and osteochondromas.

COMPLIANCE WITH ETHICAL STANDARDS

ETHICAL STATEMENT
Disclosure of potential conflicts of interest: The authors have no conflict of interests to disclose regarding the publication of this paper.
Research involving human participants and/or animals: Human tissue which was previously resected during surgery was used in this study. However, no human participants/animals were directly involved in this study.
Informed consent: Verbal informed consent for usage of previously resected tissue of study participants was obtained from all patients and/or parents.

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