Malignant transformation in an 11-year-old child with multiple hereditary exostosis

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Citation: De Stadler JL, Kruger N, Singh S, Banderker E, Dix-Peek S, Pillay K. Malignant transformation in an 11-year-old child with multiple hereditary exostosis. SA Orthop J 2021;20(3):183a-e. http://dx.doi.org/10.17159/2309-8309/2021/v20n3a8

Editor: Prof. Theo le Roux, University of Pretoria, Pretoria, South Africa

Received: August 2020

Accepted: November 2020

Published: August 2021

Funding: No funding was received for this study.

Conflict of interest: The authors declare they have no conflicts of interest that are directly or indirectly related to the research.

Abstract

Background

Multiple hereditary exostosis (MHE) is a rare autosomal dominant disorder predisposing to the development of multiple osteochondromas. Malignant transformation is an uncommon complication of osteochondromas and is especially rare in the paediatric population. Making a diagnosis of malignant transformation is recognised as a challenge globally.

Methods

We obtained informed consent and ethics approval prior to reviewing the hospital file, radiology and pathology of our index patient, as well as conducting a directed literature search.

Results

An 11-year-old male with MHE presented with new onset pain in the right leg with an associated inability to weight bear. Plain radiographs and magnetic resonance imaging (MRI) showed features consistent with malignant transformation. The child underwent a Malawer 1 resection of the proximal fibula with no complications. The pathology confirmed a grade 1 secondary peripheral chondrosarcoma (CS) arising in an osteochondroma.

The rate of malignant transformation in MHE is as high as 36.3% in select specialist tertiary centres. Ninety per cent of the resultant malignancies are chondrosarcomas. Malignant transformation before the age of 20 years is exceptional. Plain radiology is routinely used for monitoring of patients with MHE. Other modalities exist to assess for cartilage cap thickness, a much-debated criterion of malignant change. Pathology is essential for confirmation of malignant transformation as well as to exclude high grade lesions. Treatment is wide local excision (WLE) with limb-sparing surgery and long-term follow-up to detect for local recurrences.

Conclusion

The malignant transformation of osteochondromas occurs more frequently in individuals with MHE and may even arise in the paediatric population. In the presence of suspicious clinical or radiological features, en-bloc surgical resection and histopathological correlation is mandatory to make the diagnosis. We encourage a multidisciplinary team approach with collaboration between the orthopaedic surgeon, radiologist and pathologist.

Level of evidence: Level 5

Keywords: multiple hereditary exostosis (MHE), chondrosarcoma, osteochondroma, malignant transformation

Introduction

Multiple hereditary exostosis (MHE), also known as multiple osteochondromas (MO), is a rare autosomal dominant disorder with a prevalence of approximately 1 in 50 000 in the general population.[1] The majority have germline mutations in either the EXT1 or EXT2 tumour suppressor genes, which encode proteins involved in chondrocyte proliferation and differentiation.[2,3]

Osteochondromas are variably sized, benign cartilaginous neoplasms arising from the external, juxtaepiphyseal region of bones which have formed by endochondral ossification. They may be sessile or pedunculated and are composed of an external cartilage cap, underlying cortical bone, and an innermost medullary cavity which merges with that of the bone of origin.[1,4] The most frequently affected sites include the distal femur, proximal tibia and humerus.[1]

MHE is more likely to affect males and is characterised by multiple osteochondromas, often accompanied by short stature with or without angular or limb length deformities. Individuals with a family history and at least two juxtaepiphyseal long bone osteochondromas are diagnosed clinically. Genetic testing is not required. These osteochondromas may present soon after birth and continue to grow throughout childhood until the growth plates close. The majority of affected individuals are diagnosed by the age of 12 years.[1,2]

Osteochondromas are frequently painless and slow growing, mostly causing a cosmetic deformity.[4] However, the direst complication is that of malignant transformation, invariably due to a secondary chondrosarcoma (CS).[4] This transformation, as discussed later, is especially rare in children.[2]

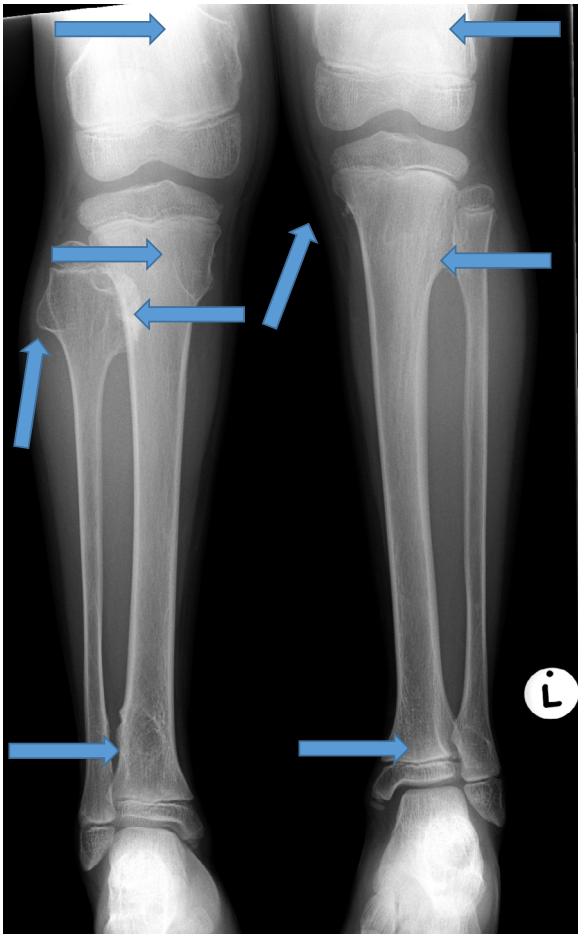

Figure 1. Lower limb frontal radiograph (9 years of age). Multiple, bilateral, sessile osteochondromas (bony exostoses). Note typical metaphyseal location with cortical and medullary continuity of the lesion and the underlying native bone.

Case report

An 11-year-old male, known to the Orthopaedic Department at Red Cross War Memorial Children's Hospital with MHE, presented with new onset right knee pain and an associated inability to fully weight bear for three days. There were no associated fevers or systemic upset. He was first diagnosed at the age of 4 years. By 10 years he had osteochondromas in both proximal humeri, both femurs (proximally and distally), both proximal tibias, the right distal tibia, the right mid-distal ulna and the right proximal fibula.

Clinically he had an antalgic gait and the pain was localised to the distal medial femoral condyle. There was no effusion. He achieved full extension, but flexion beyond 90° was resisted. Concern regarding sarcomatous change was raised on plain radiographs of the knee. Comparison with images two years prior yielded sinister interval morphological change and exuberant growth of a singular osteochondroma located at the medial metaphysis of the right proximal fibula (*Figures 1 and 2*).

Pre- and post-contrast enhanced magnetic resonance imaging (MRI) then demonstrated aggressive bone changes commensurate with malignant transformation (*Figures 3 and 4*). Most notable was the irregularity of the overlying cartilage cap and abrupt margination of an enhancing T2 hyperintense underlying intramedullary soft tissue mass.

The child underwent a Malawer 1 resection, an en bloc yet marginal resection of the proximal fibula and tumour, sparing the common peroneal nerve (CPN) and anterior tibial artery.[5] The resected specimen was large (*Figure 5a*), and the CPN had to be

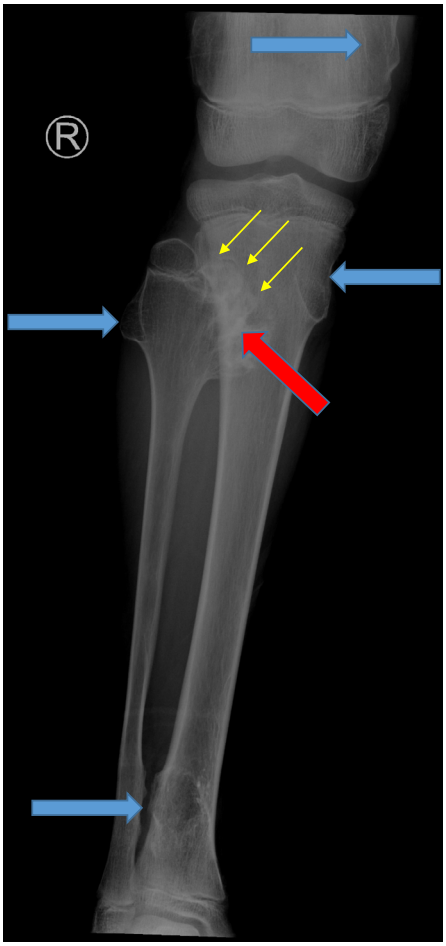

Figure 2. Frontal radiograph of the right lower limb (11 years of age). Disproportionate expansile growth of the medial metaphyseal osteochondroma of the right proximal fibula (red arrow) when compared with the other bony exostoses (blue arrows). Note increased bony sclerosis and indistinct superomedial cortex (yellow arrows).

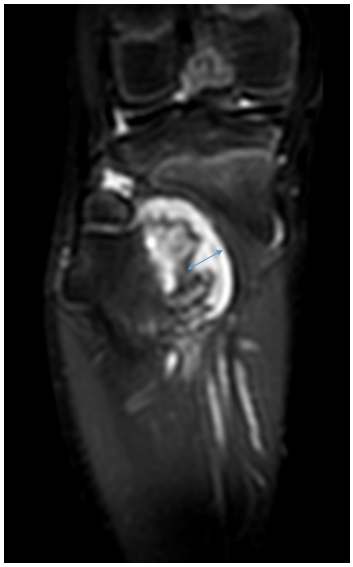

Figure 3. Coronal MRI right lower limb: T2 fat suppressed (STIR). Homogeneously T2 hyperintense cartilage cap, measuring 13 mm maximally (double-headed blue arrow), overlies the serrated bony margin. The underlying heterogeneous medullary bone lesion is sharply marginated against the fat-suppressed normal fatty marrow. Note linear as well as dot and arc low signal foci within the T2 hyperintense matrix of the medullary bone lesion.

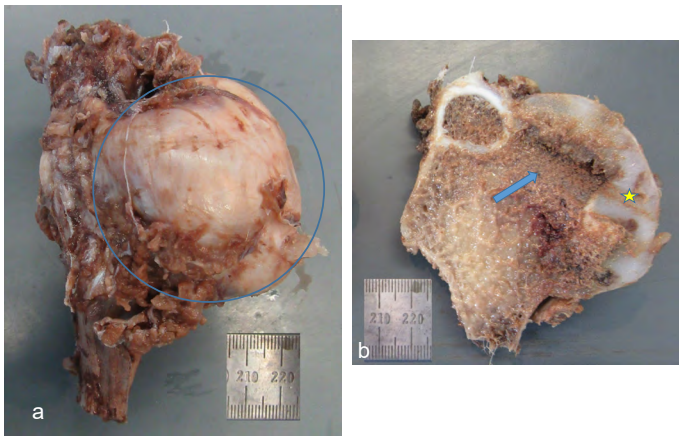

Figure 5. Right proximal fibula resection
5a. Whole specimen. The specimen measured 90 mm × 65 mm × 55 mm. Note the medial expansile osteochondroma (blue circle).
5b. Cut section. Note the irregular cartilage cap, measuring 18 mm maximally. The intramedullary soft tissue component identified radiologically is inconspicuous on gross dissection.

mobilised near the full length of the incision to ensure complete excision. The bulbous growth of the tumour both into and below the proximal tibiofibular joint notched into the adjacent tibia and made deep dissection difficult. The proximal tibiofibular joint and a small segment of adjacent tibial metaphysis were excised. The lateral collateral ligament complex, having been initially detached from the proximal fibula, was whipstitched with a 3 ethibond and reattached to the proximal lateral tibia via transosseous drill holes and periosteal suturing. The tourniquet was released to ensure meticulous haemostasis. The wound was closed in layers and a pressure dressing applied. He was discharged home in an above-knee backslab after an uneventful hospital stay.

He attended outpatient physiotherapy and was reviewed at two, four, six and ten weeks post-surgery. Wound healing was slow, with some sloughing and necrosis of the edges. By ten weeks, he was partially weight-bearing without assistance and had 10–120° range of movement at the knee. He was completely well at his five-month follow-up, and was asked to return in six months to continue annual surveillance.

Cut section of the specimen confirmed the irregularity of the overlying cartilage cap (*Figure 5b*). Microscopy confirmed a

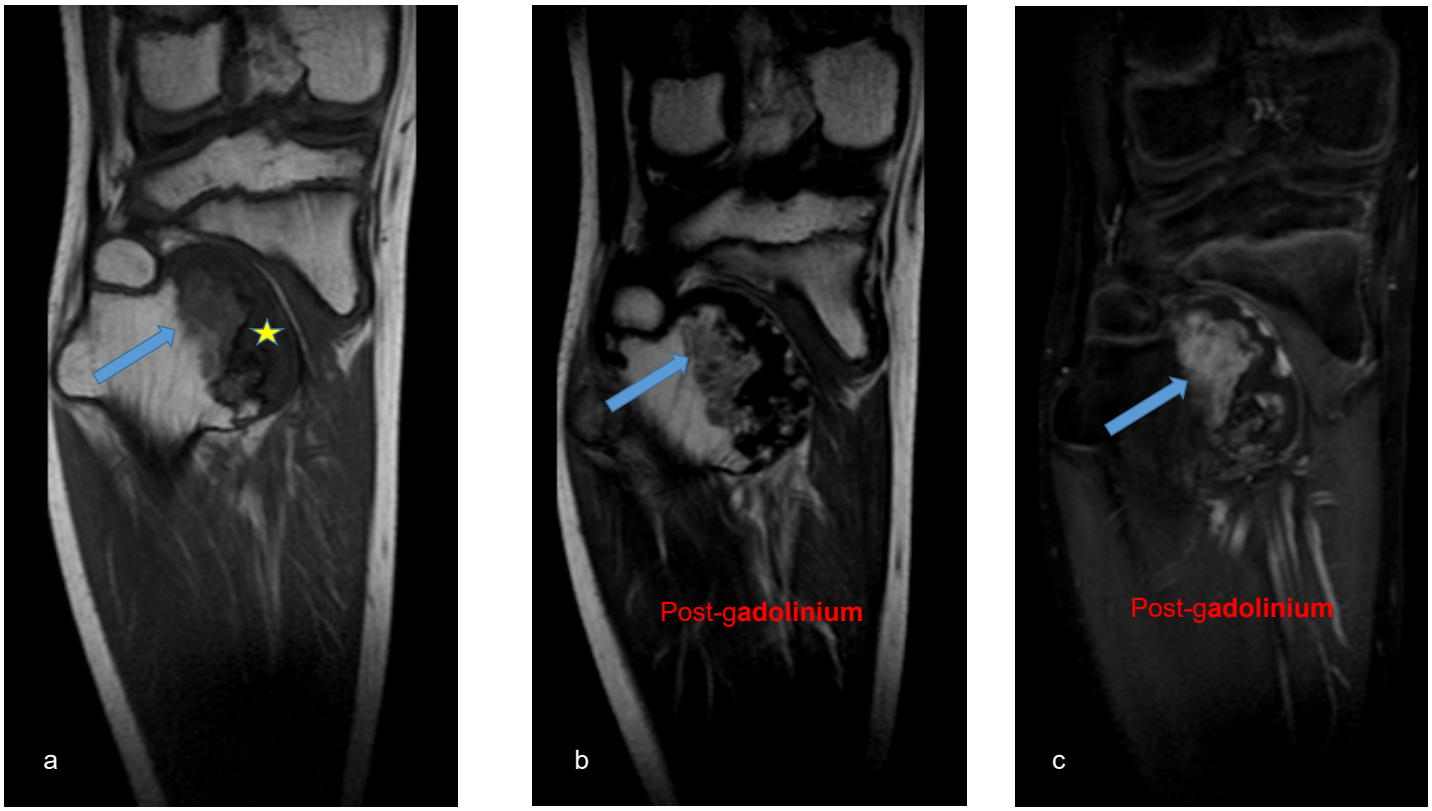

Figure 4. Coronal MRI right lower limb
4a. Pre-contrast T1-weighted image without fat suppression (FS). Note the T1 hypointense soft tissue underlying the intensely low signal cartilage cap (yellow star) sharply contrasted against the normal high signal marrow fat.
4b (without FS) and 4c (with FS) post-gadolinium T1-weighted images. Note the avid enhancement of the soft tissue component of the heterogeneous medullary soft tissue.

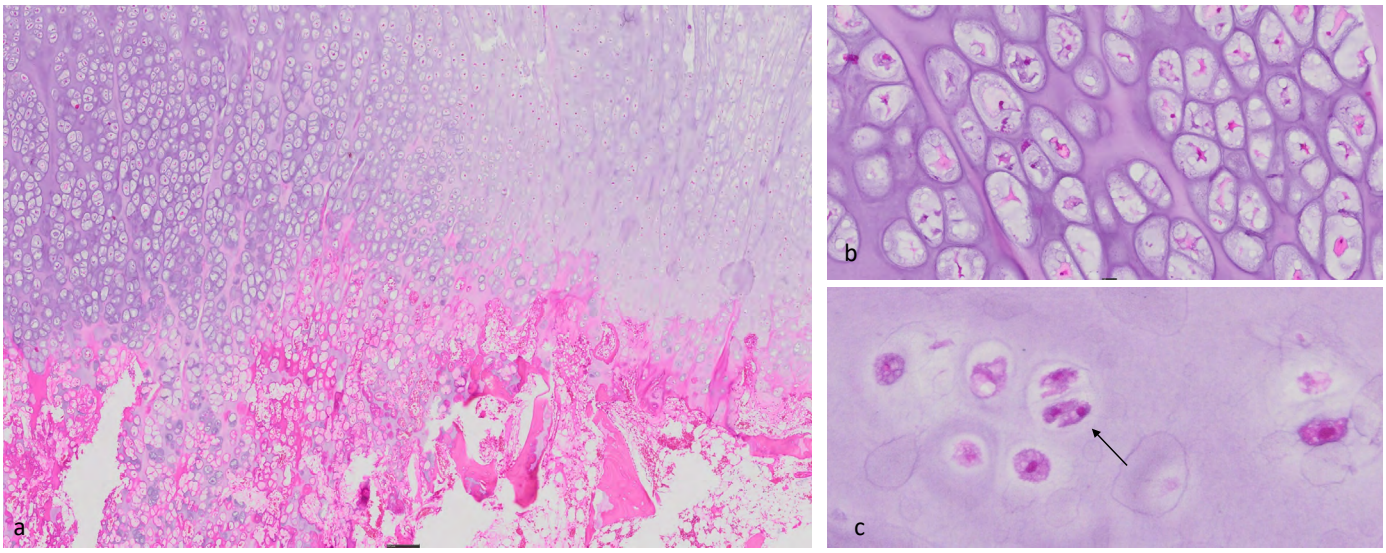

Figure 6. Microscopy
6a. Low power (4×). Note the marked increase in cellularity from right to left within the cartilage cap. Also note the replacement of fatty marrow (right) by disorganised growth plate, myxoid degeneration and irregular calcification (left), corresponding with the T2 hyperintense intramedullary mass.
6b. Intermediate power (10×). Note the increased cellularity in the areas of increased cartilage cap thickness overlying T2 hyperintense intramedullary mass.
6c. High power (20×). Occasional chondrocyte binucleation (arrow) is present. Note the lack of significant nuclear pleomorphism and mitotic activity.

grade 1 secondary peripheral CS/atypical cartilaginous tumour (ACT) arising in an osteochondroma (*Figure 6*).

Discussion

The rate of malignant transformation in MHE is between 3% and 5%,[4] although figures are as high as 36.3% in specialist tertiary centres which see a preselected high-risk population.[6] The rate is higher for centrally located lesions, for example, in the pelvis, compared to peripherally located lesions, such as around the knee.[7-9] This may be the result of early excision of peripheral lesions due to more frequent benign complications.[9]

The average time to malignant transformation is 9.8 years from initial diagnosis. Ninety per cent of the resultant malignancies are CS.[8] ACT is the preferred term for a grade 1 peripheral CS arising in the appendicular skeleton and, apart from their location, are identical to the axial counterpart grade 1 peripheral CS.[1] Making a diagnosis of a secondary CS is recognised as a challenge globally,[6] and emphasis is placed on a multidisciplinary team approach with collaboration between the orthopaedic surgeon, radiologist and pathologist.[7]

Clinical

Malignant transformation before the age of 20 years is exceptional[4] and most data are from case reports or series.[3,6,9] One may suspect malignant transformation in an adult presenting with an enlarging osteochondroma and/or pain,[2,6] or due to changes noted at annual review.[6] In contrast, growth and pain of a pre-existing lesion in the skeletally immature population are not as concerning.[3] Case reports, however, do describe mild pain, gait abnormalities, and a clinically enlarging lesion as features prompting investigation and eventual diagnosis of secondary CS in children.[3] In this case, the non-localising pain was likely a red herring prompting imaging which then raised the suspicion for further investigation. This was three months ahead of his scheduled annual review. As the excised lesion was a grade 1 ACT, later detection at this date would have been unlikely to have affected the outcome.

Radiology

Plain radiology is routinely used for monitoring of patients with MHE for malignant change. Features to note include irregularity of the surface, foci of radiolucency, heterogeneity, non-uniform calcification, erosion of the adjacent bone and an associated soft tissue mass.[4,6] MRI is necessary to determine the cartilage cap thickness in suspected cases. In addition, MRI can more accurately delineate a soft tissue mass, and allow for surgical planning.[6,8] Ultrasound scanning may also be used to measure cartilage cap thickness.[4]

While a cartilage cap thickness of 2 cm or greater has been suggested to be 100% sensitive and 98% specific for secondary CS using MRI,[8] a thickness of 1.5 cm or greater is still considered sufficiently concerning.[3,4] Furthermore, several conflicting case reports of CS show measurements between 0.5 and 1.5 cm.[6,7] Some authors propose that the cartilage cap quality may be more important than the thickness,[6] while others advocate that cartilage cap thickness should not be used as an indicator of malignant transformation in the paediatric population at all.[4] In this case, placing too much reliance on a cartilage cap cut-off of 2 cm would have resulted in misdiagnosis and delayed treatment.

Pathology

As in this case, up to 85% of secondary CS are grade 1 lesions.[4,6,7,9] Distinguishing a grade 1 peripheral CS/ACT from an osteochondroma on histology is subjective. Features such as nodularity, binucleate chondrocytes, myxoid degeneration and irregular calcifications may frequently be present in both lesions.[7] An infiltrative growth pattern[6] and invasion of surrounding soft tissue and bone cortex, when present, may assist in the diagnosis.[4] In our case, the clear transition from low to high cellularity within the thickened cartilage cap, as well as the infiltration of fatty marrow by myxomatous cartilage and irregular calcifications in the areas corresponding with the T2 hyperintensity on MRI were compatible with transformation.

Microscopy is also essential to exclude a grade 2, 3 or dedifferentiated CS by observing the lack of mitotic activity, nuclear pleomorphism and a malignant spindle cell component.[7] In addition, it is useful for subtyping, the majority of which are CS, not otherwise specified (NOS). Alternate subtypes may impact both treatment and prognosis.[10]

Management and prognosis

CS ideally require wide local excision (WLE) with limb-sparing

surgery to prevent recurrence. Care must be taken to excise the entire perichondrium and prevent myxomatous cartilage leak into the surgical bed to minimise the risk of recurrence.[3,4,6,7] Marginal excision may be considered in surgically challenging locations.[6,7] Both chemotherapy and radiotherapy are of little benefit as CS are mostly resistant.[4,6,10]

If there is uncertainty of malignant transformation, close follow-up with serial imaging and timely surgical treatment is appropriate.[2,3,8] Pre-excision biopsy is not advised, unless a high-grade malignancy is suspected.[3]

Long-term follow-up is essential to detect local recurrences, which often occur in the first five years after surgery and occur slightly more often in individuals with MHE.[6] Recurrence rates in WLEs are low, between 0% and 15%, whereas rates in marginal or intralesional resections are much higher, between 57% and 78%.[4] Regardless, annual clinical review and radiological screening, ideally MRI, is recommended for all individuals with MHE.[1,2] The majority of deaths are due to complications of a local recurrence, highlighting the need for adequate surgical excision. Importantly, repeated excisions for recurrent lesions can result in eventual progression to a higher-grade CS.[6] The frequency of follow-up of cases with prior malignant transformation is not addressed by the literature reviewed.

Conclusion

The malignant transformation of osteochondromas occurs more frequently in individuals with MHE and may even arise in the paediatric population. The diagnosis is especially challenging in this age group. In the presence of suspicious clinical or radiological features, en-bloc surgical resection and histopathological correlation is mandatory to make the diagnosis. Long-term follow-up is essential to detect recurrences. We encourage a multidisciplinary team approach with collaboration between the orthopaedic surgeon, radiologist and pathologist.

Acknowledgement

We thank Jurgen Geitner, Senior Technical Officer at the University of Cape Town (UCT) Pathology Learning Centre, for providing the whole slide images for the micrographs.

Ethics statement

Prior to commencement of the study, ethical approval was obtained from the Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town. HREC REF: 675/2020, and written informed consent was obtained from the legal guardian.

Declaration

The authors declare authorship of this article and that they have followed sound scientific research practice. This research is original and does not transgress plagiarism policies.

Author contributions

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Kruger N: Data collection, analysis, manuscript preparation, critical revision for important intellectual content and final approval of the version submitted to the journal

Singh S: Data collection, critical revision for important intellectual content and final approval of the version submitted to the journal

Banderker E: Manuscript preparation, critical revision for important intellectual content and final approval of the version submitted to the journal

Dix-Peek S: Critical revision for important intellectual content and final approval of the version submitted to the journal

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