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A rare case of adolescent Histiocytic Sarcoma

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Histiocytic sarcoma is a rare haematopoietic malignancy with an aggressive nature and poor prognosis. It occurs infrequently in children and adolescents, with only a few cases reported worldwide.

A well 14-year-old male patient presented with a slow-growing mass on his right lateral malleolus. Imaging suggested a benign tumour and an excision biopsy was performed. Morphological examination raised suspicion for a histiocytic neoplasm, which was confirmed by immunohistochemistry (CD68 and CD45 positive, CD1a, CD30 and ALK1 negative). Because of the tumour's rarity, it was sent for an international confirmatory pathological review.

Contribution: Our patient underwent a wide local resection followed by radiotherapy (50 Gy). No adjuvant chemotherapy was prescribed, and he has remained in remission 2 years following his diagnosis.

Keywords: rare; aggressive; high-grade neoplasm; unknown aetiology; poor prognosis.

Introduction

Histiocytic sarcoma (HS) is a rare haematopoietic malignancy and not a true sarcoma.[1] Derived from an overgrowth of histiocytic cells, HS is classified as one of the non-Langerhans cell histiocytoses (non-LCH) as it does not meet the phenotypic criteria for the diagnosis of LCH.[1,2]

Histiocytic sarcoma is an extremely aggressive neoplasm with an unknown aetiology and a rapidly progressive clinical course.[3] There are no known environmental or hereditary genetic factors that predispose to its development.[1] It has no gender predilection and occurs predominantly in adults, with only a few paediatric cases reported in the literature.[1,2,4,5]

Histiocytic sarcoma may occur in isolation, or in the context of another haematological malignancy, such as non-Hodgkin lymphoma, acute lymphoblastic leukaemia or myelodysplasia.[1,5] In these synchronous cases, the two entities are often clonally related. An exception is tumours that exhibit HS features in the context of acute monocytic leukaemia (a subtype of acute myeloid leukaemia), as these tumours are then not considered separate disease entities.[1]

Histiocytic sarcoma is characteristically an extranodal disease and commonly occurs in sites such as the skin, soft tissue and gastrointestinal tract.[3,5] Primary bone involvement is exceedingly rare. There is, however, no characteristic pattern of organ system involvement, and any organ may be involved.[2,4,6,7]

The clinical presentation and outcome vary from localised disease to life-threatening disseminated disease. Presenting symptoms may include extranodal masses, as well as non-specific systemic B symptoms such as fever, weight loss, anorexia and asthenia. Patients may also present with hepatosplenomegaly, lymphadenopathy, intestinal obstruction, rash and pancytopaenia.[1,3]

The differential diagnosis of HS is vast and includes, but is not limited to, inflammatory pseudotumour, follicular dendritic cell sarcoma, interdigitating dendritic cell sarcoma, malignant LCH, large cell anaplastic lymphoma, melanoma and other sarcomas.[1,3]

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Representative tissue demonstrates an infiltrative process with a diffuse growth pattern and effacement of the normal architecture.[1,8] Morphologically, large cells with an abundant eosinophilic cytoplasm and fine vacuoles may be seen. The nuclei are pleomorphic and slightly eccentric with moderately dispersed chromatin.[7] They may contain one or more small, prominent nucleoli. Birbeck granules (pathognomonic for LCH) and cellular junctions are absent on electron microscopy.

On immunohistochemical staining, the cells typically express CD68, lysozyme, CD4 and CD163, but do not express specific T and B cell markers, nor myeloid cell markers (e.g. myeloperoxidase, CD33, CD1a, S100 protein or epithelial markers).[8,9,10]

Because of its overall rarity, there is a lack of prospective randomised evidence and no standard of care.[2,4] Treatment of HS usually consists of a multimodal approach because of its aggressive nature. A distinction is made between localised (unifocal) and multisystem disease, where localised disease is generally treated with surgery with or without adjuvant radiotherapy, while multisystem disease is mostly treated with chemotherapy.[1,4]

Apart from surgery, radiation and chemotherapy, some tumours may harbour certain mutations (BRAF V600E or mutations in the MAP2K1 pathway) which may then be targeted by BRAF and MEK inhibitors.[1] The prognosis of HS, however, remains extremely poor, with disease stage, tumour number and size thought to be important prognostic indicators.[1,3]

Case presentation

A previously well 14-year-old male patient, who was a competitive swimmer, became aware of an ill-defined swelling over his right lower leg. He noticed the swelling after experiencing pain upon wearing his right flipper and first attributed the swelling to trauma while training. But instead of improving with rest, it slowly worsened with time. This progression of pain, which gradually became a sharp, severe pain upon standing, prompted his parents to seek medical care. At presentation, there were no reported B symptoms, specifically no significant weight loss and no accompanying night sweats. He was not known to have a previous or concomitant haematological neoplasm.

Clinically, there was a soft tissue mass palpable over the antero-lateral aspect of his right lower leg, with no surrounding skin or temperature changes, and no pain on palpation. This mass appeared fixed and immobile. There was no lymphadenopathy, specifically no right inguinal lymphadenopathy, and both left and right posterior tibial pulses were palpable and equal in volume. He was not pale, had no hepatosplenomegaly and had a normal cardiopulmonary examination.

A magnetic resonance imaging (MRI) of the right lower leg showed a small, ovoid, T2 hyperintense lesion within the deep intermuscular fascia between the extensor halluces longus and extensor digitorum longus muscle (Figure 1 and Figure 2). It measured 9.3 × 7.4 × 15.6 mm and demonstrated heterogeneous enhancement. Based on this, a benign peripheral nerve sheath tumour involving the deep fibular nerve was considered most likely. A complete blood count and chest radiograph revealed no abnormalities.

Our patient subsequently underwent an uneventful excision biopsy of the tumour with synchronous reconstructive surgery.

Microscopic examination of the tumour revealed skeletal muscle with a central aggregate of large, plump epithelioid cells, extending to the peripheral margins of the excision. The cells had bulky granular eosinophilic cytoplasm with large vesicular nuclei and prominent nucleoli on a mixed inflammatory background (Figure 3 and Figure 4).

On immunohistochemistry, CD68, CD45 and S100 stained positively (Figure 5) but with a proliferation index of only 10%. Further staining undertaken to better delineate the tumour excluded LCH (CD1a, CD30 and ALK1 stains were negative).

Although the proliferation index was relatively low, the immunophenotype best fitted with a non-LCH histiocytic sarcoma, and was reported as such by the local pathology laboratory. As this is an exceedingly rare diagnosis, and as

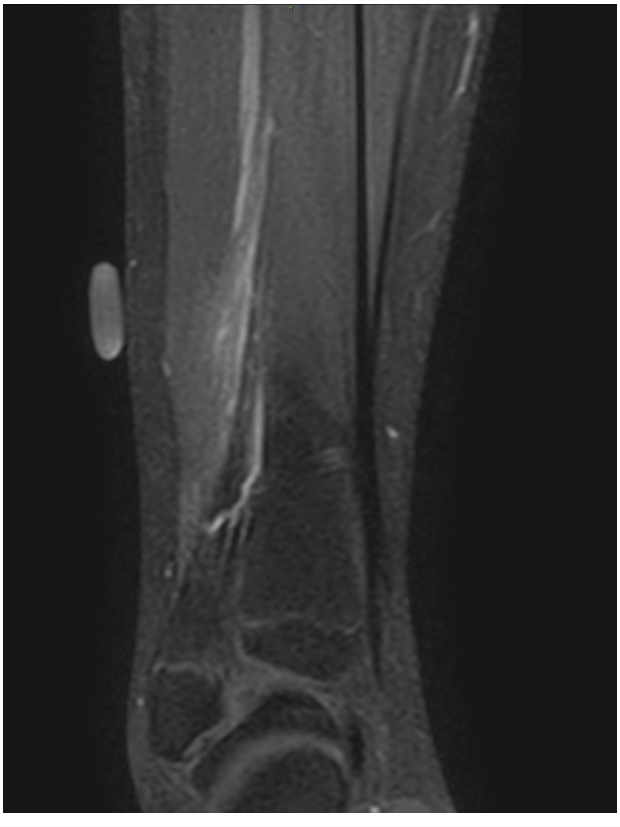


FIGURE 1: Coronal post gadolinium fat-suppressed T1 image of the right lower leg, demonstrating an enhancing soft tissue lesion in the extensor muscles of the right lower limb deep to an oil marker on the skin surface.

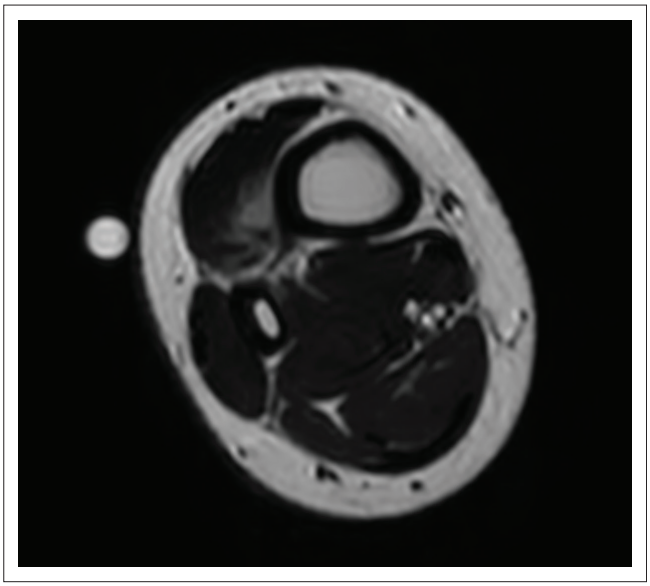


FIGURE 2: Axial T2 image of the right lower leg, demonstrating a hyperintense lesion interspersed between the extensor halluces longus and extensor digitorum longus muscle, deep to an oil marker on the skin surface.

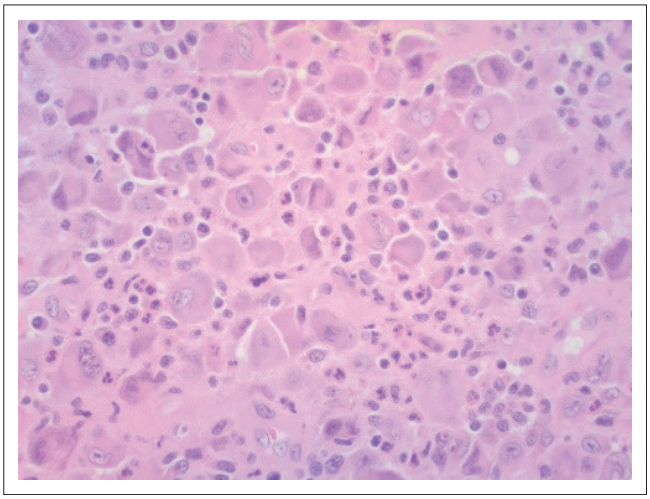


FIGURE 3: Low power photomicrograph showing plump histiocytic cells, with background lymphocytes, hematoxylin and eosin (H&E) stain 100x magnification.

they were unable to perform further confirmatory testing in South Africa, the case was sent to Cincinnati Children's Hospital Medical Centre (CCHMC) in the United States of America for review.

At CCHMC, review of the morphology revealed a high-grade neoplasm. The tumour was CD163 positive and was found to have both a CDKN2A homogenous deletion and an MTAP-BRAF rearrangement (genetic alteration where the BRAF gene is fused with the MTAP gene leading to activation of the MAPK pathway potentially driving cancer development), thus confirming the diagnosis of a histiocytic sarcoma. It was noted, however, that the low proliferation index and low mitotic rate of the tumour were not typical of an HS. Cincinnati Children's Hospital Medical Centre described a similar case in a teenager who had previously been diagnosed with a malignant histiocytic neoplasm (LCH subtype). The tumour had a low proliferation index and an MTAP-BRAF rearrangement (similar to our patient), but who remained

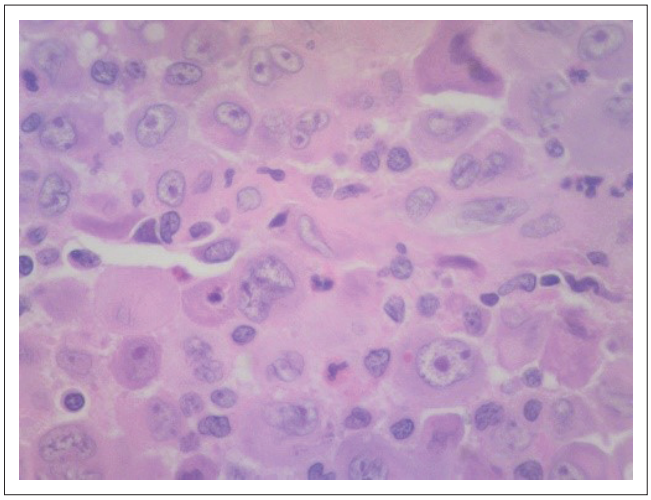


FIGURE 4: High power photomicrograph showing a plump epithelioid histiocytic cell with atypical nuclei, hematoxylin and eosin (H&E) stain 400x magnification.

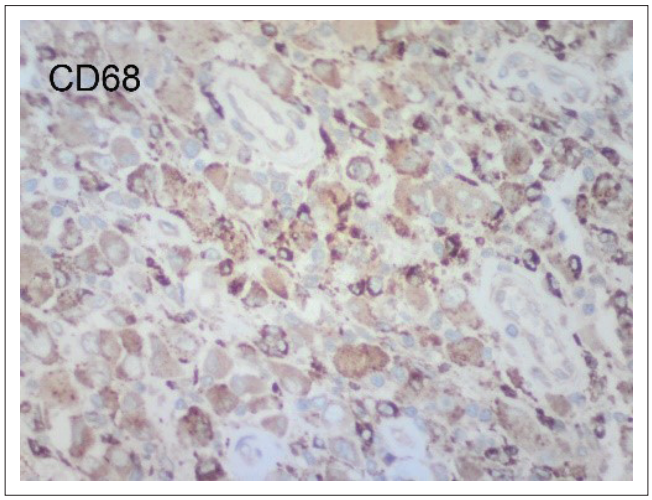


FIGURE 5: Positive CD68 stain.

in remission 3 years after complete surgical resection with no adjuvant chemotherapy. Thus, CCHMC proposed that we classify our patient's tumour as a histiocytic sarcoma with an uncertain malignant potential.

After receiving feedback from CCHMC and after a multidisciplinary discussion, our patient underwent a further wide local resection of the surgical site and tumour bed with a vascularised anterolateral thigh free flap to cover the tissue defect (Figure 6). Following this second resection, the excised soft tissue and its margins were confirmed to be clear of disease. A full body fludeoxyglucose-18 (FDG) positron emission tomography (PET) scan carried out thereafter was consistent with completely resected local disease and did not show any evidence of metastatic disease. A bone marrow aspirate and trephine biopsy were also performed, which showed a normocellular, haemopoietically active marrow with no evidence of disease infiltration.

Our patient received radiotherapy in the form of volumetric modulated arc therapy to the tumour bed plus a margin. The dose of the radiotherapy given was 50 Gy in 25 fractions. He experienced mild skin erythema during treatment, which



Source: Post surgical photograph of right lower leg, by J.A.L. du Toit, Sandton Mediclinic Hospital, South Africa, 2023. Used with permission. All rights reserved. No unauthorised duplication allowed.

FIGURE 6: Vascularised anterolateral thigh free flap.

resolved soon after the completion of therapy, and no other acute side effects were noted. No adjuvant chemotherapy was prescribed.

Our patient attends regular follow-up clinic visits and undergoes routine imaging to assess for local and distant disease relapse. He remains clinically well with a normal physical examination. A computed tomography (CT) chest carried out a year after diagnosis was normal. The most recent MRI of his right lower leg revealed no evidence of residual or recurrent tumours. He is now more than 24 months post-diagnosis, with no long-term side effects from his surgery or radiation. He has retained full function of his right ankle and has returned to his vigorous swimming regimen.

Given the unpredictable nature of HS and the uncertainty regarding the tumour's malignant potential, patient follow-up (with imaging) will continue every 4–6 months for the next 5 years (minimum).

Discussion

Histiocytic sarcoma is a very rare and aggressive haematopoietic malignancy which occurs uncommonly in the paediatric population.[1,2,4,5] We present a young adolescent male patient with a confirmed histiocytic sarcoma thought to have an uncertain malignant potential. He underwent complete surgical excision and radiotherapy and remains in remission more than 24 months after diagnosis.

Owing to the rarity of this tumour, the time to diagnosis of HS in our patient was protracted and required an international review. Apart from the immunohistochemical stains (CD163, CD68 and CD45) staining positive, review of the tumour identified both a CDKN2A homogenous deletion (found in various cancers) and an MTAP-BRAF rearrangement, which is thought to lead to resistance to certain therapies (i.e. BRAF inhibitors). The definite prognostic factor of this rearrangement is, however, still uncertain, and more research is needed to understand the prevalence, clinical significance and optimal treatment strategies for HS with MTAP-BRAF rearrangements.

In a previously published case study, a 16-year-old female patient with a rapidly growing subcutaneous thigh mass was diagnosed with HS. The tumour demonstrated an MTAP-BRAF fusion transcript with a modestly elevated proliferation index (up to 20%). She underwent a surgical resection with negative margins and is disease-free 3 years post-resection.[11] As in our patient, the lower Ki-67 proliferation rate also appeared to correlate with a more indolent behaviour, despite its high-grade morphology.

Because of the rarity and difficulties in the diagnosis of HS, there are only a limited number of clinical studies and case reports available (mostly including the adult population). From these studies and reports, poor prognostic factors may include: (1) an increased tumour size and advanced stage; (2) if the tumour is multifocal or metastatic; (3) if it has been incompletely resected or has positive margins; and (4) if HS occurs in combination with a co-existing malignancy.[4,5,10] There is a paucity of paediatric data, but published case reports suggest that these prognostic factors may also apply to the paediatric population.[12,13,14] These prognostic factors are not, however, always predictive of patient outcomes.[4,5,10,12,13,14]

Conclusion

This case report demonstrates that HS is not always an aggressive disease and highlights the uncertainties regarding the full spectrum of this tumour's behaviour. Further research is needed to determine whether a subgroup of patients may fare better and to understand the reasons behind this. Considering the possible prognostic factors, it is essential to ascertain whether underlying tumour biology, proliferation index and/or individual patient genetics play a significant role.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article. The author, D.R., serves as an editorial board member of this journal. The peer review process for this submission was handled independently, and the author had no involvement in the editorial decision-making process for this manuscript. The author has no other competing interests to declare.

Authors' contributions

All authors, N.B., K.G.B., S.L.N., H.S., O.T., D.J.M.F., J.A.L.d.T. and D.R., contributed to the writing of this case report. N.B. was involved in the conception, supervision and preparation of the first draft, as well as reviewing and editing the report. In addition to being part of the multidisciplinary team that

initially managed this patient, all co-authors contributed to the first draft of the case study: S.L.N. worked on the histopathology section; D.R. contributed to the radiation section; H.S. addressed the plastic surgery section; and D.J.M.F. and J.A.L.d.T. focused on the orthopaedic section. O.T. contributed to the imaging report for this patient, while K.G.B. helped to address the medical management. Following these contributions, all authors, N.B., K.G.B., S.L.N., H.S., O.T., D.J.M.F., J.A.L.d.T. and D.R., assisted with editing and collectively discussed the results and approved the final version for submission and publication.

Ethical considerations

Ethical clearance to conduct this study was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (reference no.: M250163). Written patient assent and parental consent were obtained prior to the submission of this article.

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Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its references.

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