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CASE REPORT

A rare case of paediatric histiocytic sarcoma of the maxilla and mandible

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Histiocytic sarcoma is an extremely rare malignant neoplastic proliferation of the haematopoietic cells. Very few cases have been reported in the paediatric age group. Imaging features have been rarely described in the literature. It can involve any region of the body; however, it most commonly involves the lymph nodes. Its imaging appearance can mimic lymphoproliferative disorders; however, with the advent of new immunohistochemical markers, the diagnosis of HS has become more reliable. We report an unusual case of primary bone involvement by HS with multiple lesions in the facial bones of a 2-year-old female who presented with tooth and mandibular tenderness.
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Introduction

Histiocytic sarcoma (HS) is an extremely rare and high-grade malignant neoplastic proliferation of the haematopoietic cells, showing features of mature histiocytes. A handful of cases have been reported to date in children. The diagnosis of HS is a clinical and histopathological challenge. Many cases in the past have been wrongly diagnosed as lymphomas, leukaemias or carcinomas.[1] Since the advent of new and more specific immunohistochemical markers, the diagnosis of HS has become more precise and reproducible. We report an unusual case of primary bone involvement by HS with multiple lesions in the facial bones of a 2-year-old female who presented with tooth and mandibular tenderness.

Case report

A 2-year-old female presented with a 2-day history of a tender intraoral swelling and fever. She did not have any significant medical history. She had a few prominent lymph nodes only in the neck, which were presumed to be reactive likely owing to fever and intraoral swelling. When the patient presented to the Accident and Emergency Department, the initial impression following the assessment by the maxillofacial team was that of an infected eruption cyst. Subsequently, under anaesthetic, a soft palpable pink-to-purple mass which started to bleed on minimal exploration was seen associated with the left second upper molar deciduous tooth. Before attempting to biopsy the lesion, it was decided, after discussion with the paediatric radiology team, to perform MRI and CT to determine the extent of the lesion and to rule out a haemangioma. Therefore, the patient was immediately transferred to the imaging department and an MRI with contrast followed by a plain CT was performed under general anaesthesia.

MRI showed a mass isointense to slightly hyperintense on T_1 and intermediate-to-low signal on T_2 compared with brain parenchyma, measuring 3.6×2.6 cm (Figure 1a). Multiple mandibular lesions and a mass in the right maxillary sinus were also noted (Figure 1a,b). The primary mass demonstrated intense homogeneous

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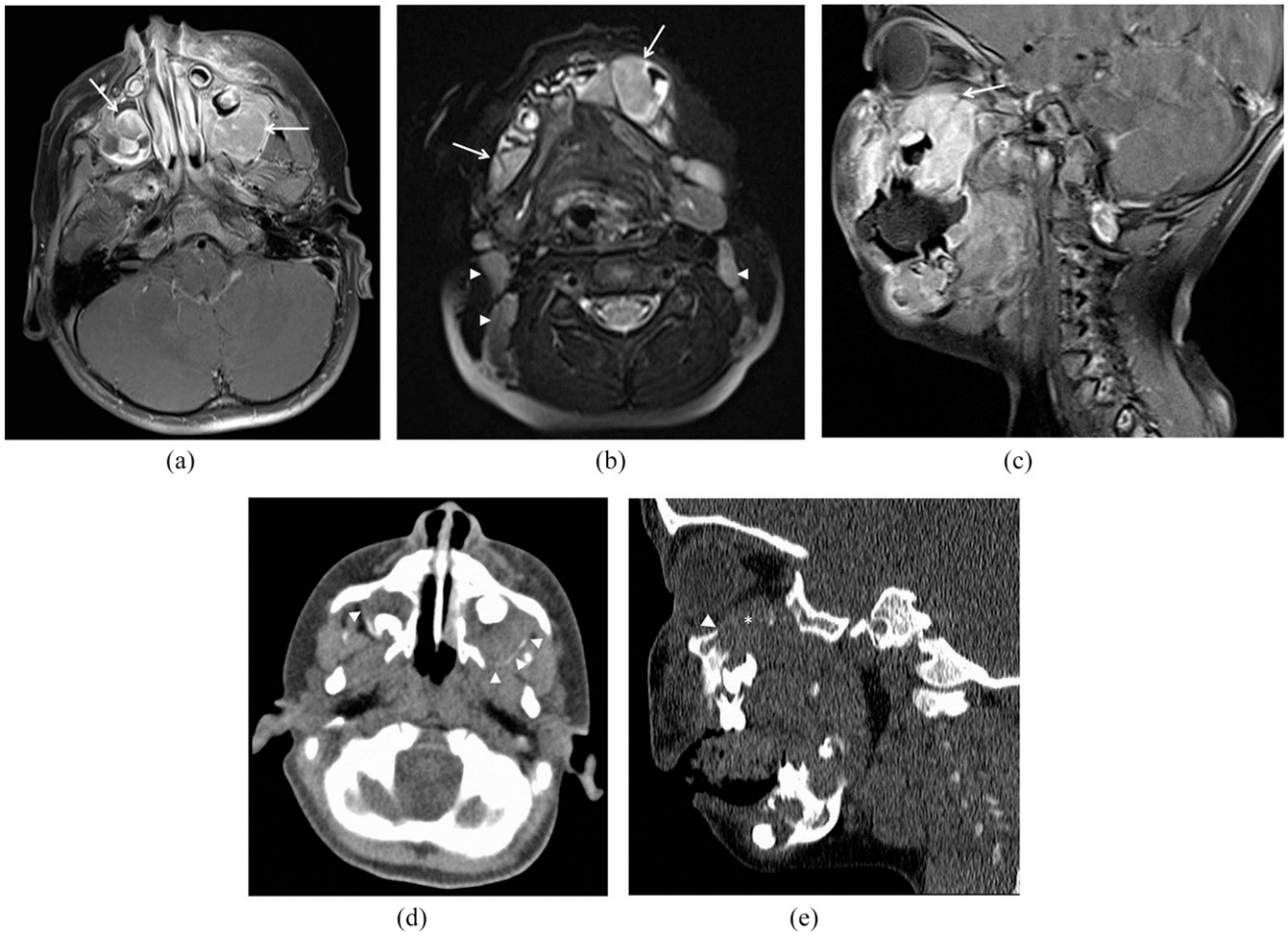

Figure 1 (a–c) MRI and (d, e) CT scan of the face. (a) Axial post-contrast T_1 fat-saturation MRI showing that the bilateral maxillary lesions in axial T_1 (arrows) are larger on the left. (b) Axial T_2 fat-saturation MRI showing multiple mandibular lesions (arrows) and enlarged lymph nodes (arrowheads) in the neck. (c) Sagittal post-contrast T_1 fat-saturation image showing homogeneous enhancement of the maxillary and mandibular mass with extension through the floor of the orbit causing mild mass effect on the inferior rectus muscle (arrow). (d) Axial CT showing a mass around the tooth and expansion of the maxillary sinuses with thinning and erosion of the posterolateral wall of the bilateral maxillary sinus (arrowheads). (e) Sagittal CT showing the edge of the destroyed floor of the orbit (arrowhead) due to mass in the maxillary sinus (asterisk).

enhancement on post-contrast sequences (Figure 1c). The mass had expanded and filled the entire left maxillary sinus and had extended into the floor of the orbit with mild mass effect on the extraocular inferior rectus muscle, highlighting its aggressive nature (Figure 1c). Multiple enlarged lymph nodes in the neck were subsequently noted, which had similar signal characteristics to the soft-tissue mass in the mandible and maxilla (Figure 1b) and also displayed intense post-contrast enhancement.

Non-contrast CT also demonstrated multiple lesions involving the maxilla and mandible (Figure 1d,e), which seemed to be associated with fully erupted deciduous molar teeth. Both maxillary sinuses were expanded more on the left side with erosion and thinning of its posterolateral wall (Figure 1d). The roof of the left maxillary sinus is significantly destroyed (Figure 1e).

In the presence of multiple lesions in the mandible associated with fully erupted deciduous molars, initial considerations were of atypical odontogenic tumours. The solid appearance with aggressive bone erosions and lymph node involvement favoured a malignant process, and the possibility of metastatic lesions was then considered. Consequently, our main differentials were of a haematological malignancy and Langerhans cell histiocytosis (LCH).

After the MRI, the same day, whilst the patient remained under anaesthetic, the maxillofacial team returned to theatre and proceeded to biopsy the lesion in the left maxilla. The final histology (Figure 2a–c) confirmed a high-grade malignant tumour consistent with HS with an immunohistochemical phenotype characterized by positivity for CD4, CD163, CD56, CD31, CD43, CD68 (PGM-1 and KP1) and focal positivity for S-100 (Figure 3a,b), but negativity for myeloperoxidase, B-cell markers (CD20, CD79, PAX5), T-cell markers (CD3, CD7) and Langerhans cell markers (CD1a and Langherin).

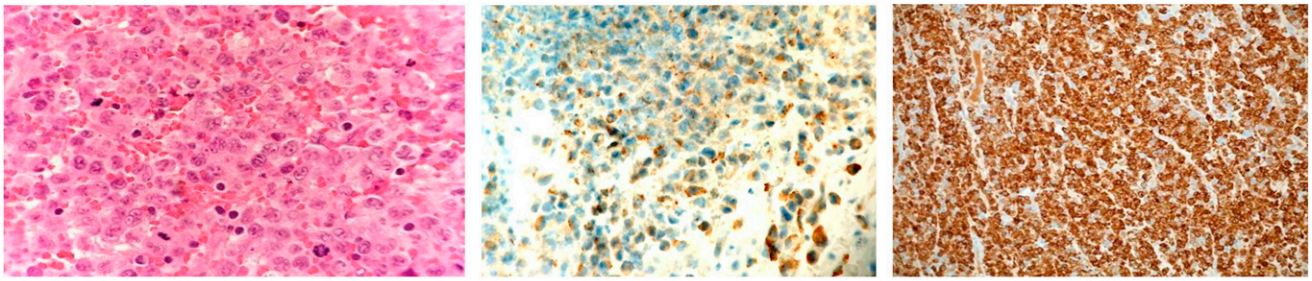

Figure 2 (a) Haematoxylin and eosin stain showing sheets of epithelioid cells that have an abundance of pink cytoplasm, with prominent nucleoli and a high nuclear/cytoplasmic ratio, showing marked cytologic atypia and numerous atypical mitotic figures. (b) Immunohistochemistry demonstrated the majority of tumour cells were positive for the histiocytic marker CD68, showing granular cytoplasmic staining, (c) and near 100% of cells were positive for CD163, a specific histiocytic lineage marker, which led to the diagnosis.

The patient was subsequently treated with two cycles of cytarabine, daunorubicin, etoposide (ADE) chemotherapy and two cycles of high-dose cytarabine chemotherapy, which led to significant improvement. Follow-up after 3 months showed a decrease in the size and extent of the maxillary and mandibular lesions (Figure 3a–c). The neck lymph nodes also decreased in size and number (Figure 3c).

Discussion

HS is an extremely rare malignant proliferation defined in the World Health Organization classification as a neoplastic proliferation with features of histiocytes.[2,3] Histiocytes are of two types: macrophage/monocyte and dendritic cell type. HS develops from macrophage histiocytes, which are phagocytes that destroy harmful proteins, viruses and bacteria in the body. Dendritic cell histiocytes stimulate the immune system. Their proliferation gives rise to LCH, Langerhans cell sarcoma and dendritic cell sarcomas.[2,3]

Owing to the rarity of HS cases, typical demographics have not been determined. No age group is spared; however, most cases reported have occurred in a bimodal age distribution with a small peak at 0–29 years and a larger peak at 50–69 years.[1,2] The most common site of involvement are lymph nodes, but many sites such as the gastrointestinal tract, spleen, soft tissue and skin have been described.[1–8] Atypical sites including the head and neck, salivary glands, lung, breast, liver, kidney, uterus, central nervous system and bone marrow have been reported.[1–8] HS in paediatric patients are rare, with only a handful of reported cases.[3] Bone marrow involvement as a localized disease and in disseminated cases has also been described; however, facial involvement has not been previously reported. Our patient was a female, although there is a male predominance in the reported literature.[2]

HS is an aggressive neoplasm that usually presents at an advanced clinical stage. Presentation depends on the site of involvement: localized pain, swelling and lymph

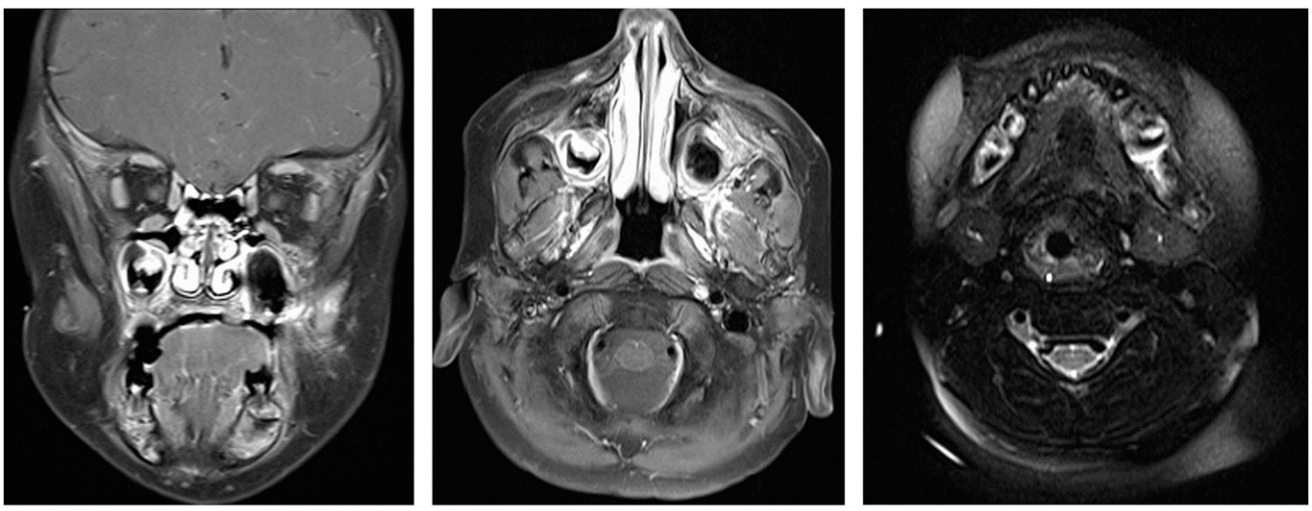

Figure 3 (a–c) MRI after 3 months of therapy. (a, b) Coronal and axial post-contrast axial T_1 fat saturation showing a significant decrease in the size of the mandibular and maxillary lesions. (c) Mandibular lesions and neck lymph nodes have significantly decreased.

node enlargement. Patients can also present with fever, night sweats, fatigue, weight loss and weakness.[1,2] Skin lesions, intestinal obstruction and hepatosplenomegaly have also been reported.[2] Our patient presented with localized pain and swelling in the maxillary region, which were initially thought to represent tooth ache related to a tooth abscess.

The diagnosis of HS requires a biopsy including the morphological assessment of the tumour on haematoxylin and eosin-stained sections and immunohistochemical phenotyping. Morphologically, the tumour cells have abundant eosinophilic cytoplasm. The nuclei are large with prominent nucleoli. They have a high nuclear/cytoplasmic ratio, show marked cytologic atypia and numerous atypical mitotic figures.[2,3] Birbeck granules on electron microscopy are essentially absent, which helps in distinguishing HS from Langerhans and dendritic cell tumours.[3]

HS tumours can express one or more histiocytic markers including CD68, lysozyme, CD163 and S-100 and do not express B-cell, T-cell or myeloid markers.[1–3,8] In the present case, the tumour was positive for CD68 (Figure 2b), which is a marker of macrophage/histiocytic deviation.[2] This has good reproducibility showing granular cytoplasmic staining, but positive staining with CD68 can also be seen in other cell types, mainly neutrophils. CD163 (Figure 2c) is a more recently discovered immunohistochemical marker of histiocytic lineage (haemoglobin scavenger receptor).[9] CD163 is a highly specific macrophage/histiocytic marker and thus can have significant diagnostic utility in separating HS from other tumours.[1] HS can show positive labelling with S-100 protein, which is often weak and patchy rather than uniform.[1–3]

More cases of HS have been previously reported; however, following the availability of these immunohistochemical markers, many had to be reclassified as representing anaplastic large B-cell lymphoma, peripheral T-cell lymphoma associated with haemophagocytic syndrome or lymphoma with associated reactive macrophages.[2,3] The differential diagnosis of HS on imaging, irrespective of the primary site, is wide and includes metastatic carcinoma, dendritic cell neoplasm and large B- or T- cell lymphoma, especially anaplastic large-cell lymphoma and diffuse large-cell lymphoma, malignant melanoma, undifferentiated large-cell carcinoma, monocytic leukaemia, soft-tissue sarcomas and infectious disease. Histological examination and an appropriate panel of immunohistochemical markers permit differentiation between these differential diagnoses.[1,2,4]

HS can be associated with lymphoma and leukaemia, either occurring simultaneously or after a delay of 2 months–17 years.[2] Takahashi et al[2] have noted a number of cases of HS preceding the diagnosis of lymphoma. Those that occur in children are usually lymphoblastic lymphoma/leukaemia. Sometimes, the histiocytic lesions share molecular/cytogenetic features with the original leukaemia or lymphoma, suggesting that there may have been progression from previous disease.[5] Feldman et al[6] noted seven cases of HS following follicular lymphoma and found that both malignancies had a common clonal origin.

Imaging features have been rarely described. Imaging, like clinical presentation, largely depends upon the site of involvement. In our case, lymph nodes in the neck were involved, which were enlarged and showed avid post-contrast enhancement. Although not performed in our case, studies also demonstrate that involved lymph nodes are associated with avid fluorine-18 fludeoxyglucose-positron emission tomograpy/CT uptake with maximum standardized uptake value ranging from 12 to 23.[1]

HS in the brain has been reported. On MRI, the solid component appears isointense on both T_1 and T_2 weighted images. Cystic changes can also be present and following contrast administration, the lesion shows avid enhancement. The solid portion can also show slight restricted diffusion on diffusion-weighted imaging.[8] In bones, HS appears as a destructive lesion with an extraosseous soft-tissue component. Multifocal lesions in the spine have been described, although our patient had multiple lesions involving the maxilla and mandible, which have not been previously described in the paediatric or adult population.

The suspicion of LCH should be considered in the differential diagnosis of HS with bone involvement, which is far more common in the paediatric population. Lymph node involvement can also confuse a diagnosis with non-Hodgkin's lymphoma.[1] On CT and radiographs, lesions in the maxilla and mandible associated with teeth could also mimic odontogenic tumours. In our case, CT and MRI both helped in the assessment of the solid enhancement of the soft-tissue component and CT showed the aggressive bony erosion, which helped in raising the suspicion of a possible malignant process that was subsequently biopsied and proven to be an HS.

HS grows quickly and aggressively; hence, it has a poor prognosis and often leads to a short survival period.[8] No standard therapy has been developed owing to its rarity. Usually, surgical resection with radiation therapy for localized disease and combination chemotherapy for multifocal disease are administered.[5] Most patients die of progressive disease within 2 years. There are reports of patients who respond to treatment and have a relatively indolent clinical course.[10] Localized disease shows a better prognosis.[6,10] Treatment protocols have evolved over time and recent studies suggest that a combination of radiotherapy and chemotherapy can be useful.[11] In our case, the patient was treated with ADE chemotherapy regime, which is often used for patients with acute myeloid leukaemia. After three cycles of treatment over a 3-month period, there was significant interval improvement, suggesting a good response to treatment. At the time of the report, the patient was still undergoing treatment.

HS is an extremely rare lesion. It is less common in bones and even rarer in the paediatric population.

Although HS is indistinguishable from other aggressive malignant lesions on imaging alone, imaging plays an important role in determining the aggressiveness of the lesion and its extent. Accurate histological diagnosis with the use of immunohistochemistry is also vital in order to implement an effective treatment plan.

References

1. Saboo SS, Krajewski KM, Shinagare AB, Jagannathan JP, Hornick JL, Ramaiya N. Imaging features of primary extranodal histiocytic sarcoma: report of two cases and a review of the literature. *Cancer Imaging* 2012; **12**: 253–8. doi: http://dx.doi.org/10.1102/1470-7330.2012.0029
2. Takahashi E, Nakamura S. Histiocytic sarcoma: an updated literature review based on the 2008 WHO classification. *J Clin Exp Hematop* 2013; **53**: 1–8.
3. Buonocore S, Valente AL, Nightingale D, Bogart J, Souid AK. Histiocytic sarcoma in a 3-year-old male: a case report. *Pediatrics* 2005; **116**: e322–5. doi: http://dx.doi.org/10.1542/peds.2005-0026
4. Kaushal R, Jambhekar NA, Rao S, Raju S, Suryawanshi P, Shet T, et al. Primary extranodal histiocytic sarcoma of lumbar spine. *Skeletal Radiol* 2012; **41**: 231–5. doi: http://dx.doi.org/10.1007/s00256-011-1228-x
5. Chalasani S, Hennick MR, Hocking WG, Shaw GR, Lawler B. Unusual presentation of a rare cancer: histiocytic sarcoma in the brain 16 years after treatment for acute lymphoblastic leukemia. *Clin Med Res* 2013; **11**: 31–5. doi: http://dx.doi.org/10.3121/cmr.2012.1092
6. Feldman AL, Arber DA, Pittaluga S, Martinez A, Burke JS, Raffeld M, et al. Clonally related follicular lymphomas and histiocytic/dendritic cell sarcomas: evidence for transdifferentiation of the follicular lymphoma clone. *Blood* 2008; **111**: 5433–9. doi: http://dx.doi.org/10.1182/blood-2007-11-124792
7. Shen XZ, Liu F, Ni RJ, Wang BY. Primary histiocytic sarcoma of the stomach: a case report with imaging findings. *World J Gastroenterol* 2013; **19**: 422–5. doi: http://dx.doi.org/10.3748/wjg.v19.i3.422
8. Bai J, Li G, Shen M, Sui D, Lin S. Primary central nervous system histiocytic sarcoma mimicking glioma. *Neurol India* 2014; **62**: 684–5. doi: http://dx.doi.org/10.4103/0028-3886.149409
9. Vos JA, Abbondanzo SL, Barekman CL, Andriko JW, Miettinen M, Aguilera NS. Histiocytic sarcoma: a study of five cases including the histiocyte marker CD163. *Mod Pathol* 2005; **18**: 693–704. doi: http://dx.doi.org/10.1038/modpathol.3800346
10. Hornick JL, Jaffe ES, Fletcher CD. Extranodal histiocytic sarcoma: clinicopathologic analysis of 14 cases of a rare epithelioid malignancy. *Am J Surg Pathol* 2004; **28**: 1133–44. doi: http://dx.doi.org/10.1097/01.pas.0000131541.95394.23
11. Patnaik A, Mishra SS, Senapati SB. A rare case of primary extranodal, extradural histiocytic sarcoma of the thoracic spine and review of literature. *Surg Neurol Int* 2012; **3**: 96. doi: http://dx.doi.org/10.4103/2152-7806.100183