Recurrent Multisystem Langerhans Cell Histiocytosis with Skull-Predominant Manifestations: Case Report and Review of the Literature

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Background

- Langerhans cell histiocytosis (LCH) is a hematologic disease process where Langerhans cells proliferate as a localized or disseminated disease process, most commonly occurring in children under 15 years of age with an incidence rate of 4.5 per million children.
- One variant of LCH, eosinophilic granuloma, is most commonly identified in lesions within the skull as a single or multiple osteolytic lesions which may be painful.
- We present a case of a child with a history of disseminated LCH with recurrence in the skull.

Materials & Methods

- A review of the patient's electronic medical record was undertaken and radiologic and histologic findings were reviewed.
- A literature search was conducted using appropriate key words.

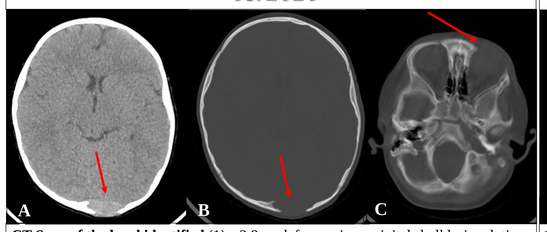
Case Report

- The patient is a 5-year-old boy. He presented initially at age 2 with left eye swelling.
- Imaging of his head revealed (1) a lesion in the right orbit, 2.6 cm, with mass effect on the left globe, and (2) a 2.8 cm left superior occipital skull lesion, lytic.
- An excisional biopsy of skull lesion revealed LCH with a BRAF V600E mutation.
- Subsequent right iliac crest bone marrow biopsy revealed involvement. The working clinical diagnosis was multisystem LCH.
- He was treated with chemotherapy. He was initially treated via LCH III (Arm A) and transitioned to a BRAF inhibitor (vemurafenib) in 07/2020 due to disease persistence. Scans in 5/2021 showed no clear evidence of recurrent or persistent disease, although there was a subtle asymmetric T2 hyperintensity within the left orbit. Treatment was resumed per LCH III on 6/17/2021 (Arm B). He completed chemotherapy on 7/14/2022.
- Scans showed no clear evidence of recurrent or persistent disease, although there was a subtle asymmetric T2 hyperintensity within the left orbit.
- He subsequently, he developed frequent headaches and fatigue along with a new, palpable bump on his head.
- CT and MRI imaging of his skull in 06/2024 revealed (1) a new left parietal skull lesion, lytic, avidly contrast-enhancing lesion, 2.1 cm, suspicious for an eosinophilic granuloma, (2) decreased size of the left orbit soft tissue density mass, superior extraconal station, and (3) brain volume loss with progressive T2 FLAIR abnormality in the bilateral cerebellar hemispheres along with the dentate nuclei, possibly representing neurodegeneration in the setting of LCH.
- The left parietal lesion was resected in 07/2023 and histologic and immunohistochemical evaluation revealed recurrent LCH consistent with relapsed multisystem LCH. The lesion appeared to be retained within periosteum and separately submitted adjacent dura was negative.
- Clofarabine chemotherapy was initiated with treatment extending through 03/08/2024.
- Imaging studies have been stable.

Results

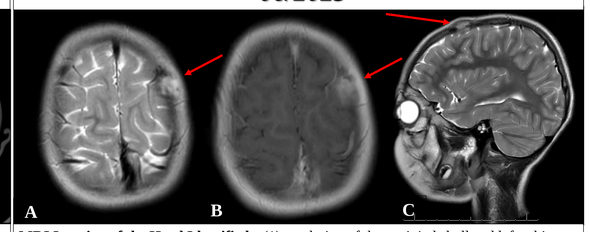
Head Imaging

05/2020



CT Scan of the head identified (1) a 2.8 cm left superior occipital skull lesion, lytic and (2) a lesion in the right orbit, 2.6 cm, with mass effect on the left globe. **A.** Standard CT scan. **B-C.** CT with Bone Windows, all coronal sections.

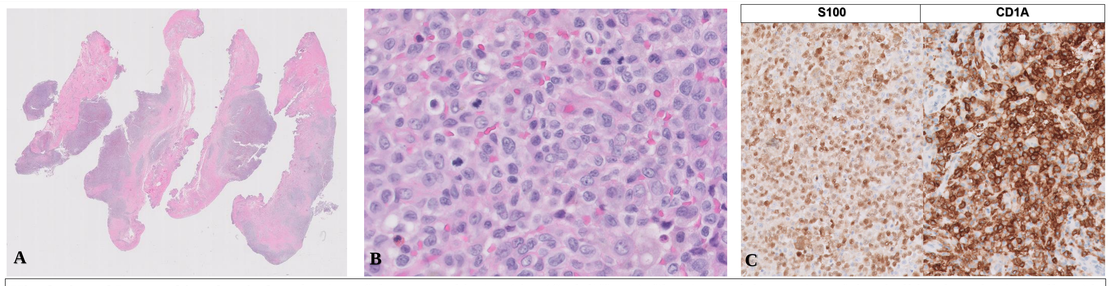
06/2023



MRI Imaging of the Head Identified a (1) resolution of the occipital skull and left orbit lesions and (2) new, left parietal skull lesion, lytic, avidly contrast-enhancing lesion, 2.1 cm. **A.** T2 – Coronal, **B.** T1 with Contrast – Coronal, **C.** T2 – Sagittal.

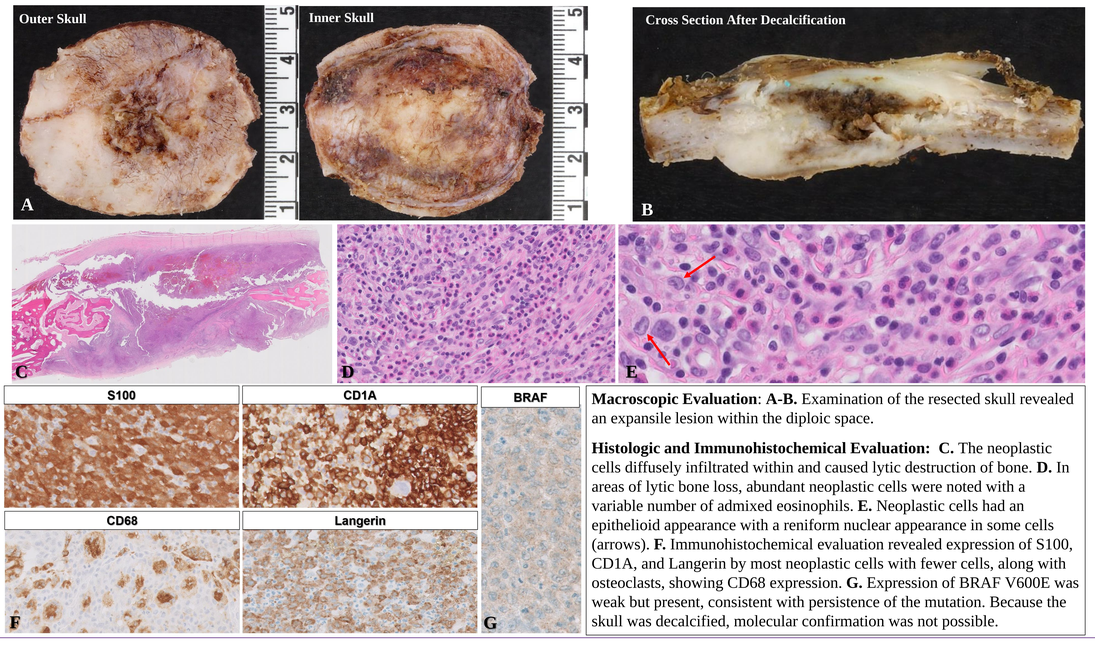
Neuropathologic Evaluation

05/2020



Histologic and Immunohistochemical evaluation of the resected lesion identified diffuse infiltration and destruction of the skull by dyscohesive cells with a reniform nucleus and moderate eosinophilic cytoplasm. Immunohistochemical evaluation identified expression of S100 and CD1A. Combined features were diagnostic of Langerhans cell histiocytosis. Molecular evaluation revealed a BRAF V600E mutation.

07/2023



Macroscopic Evaluation: **A-B.** Examination of the resected skull revealed an expansile lesion within the diploic space.

Histologic and Immunohistochemical Evaluation: C. The neoplastic cells diffusely infiltrated within and caused lytic destruction of bone. **D.** In areas of lytic bone loss, abundant neoplastic cells were noted with a variable number of admixed eosinophils. **E.** Neoplastic cells had an epithelioid appearance with a reniform nuclear appearance in some cells (arrows). **F.** Immunohistochemical evaluation revealed expression of S100, CD1A, and Langerin by most neoplastic cells with fewer cells, along with osteoclasts, showing CD68 expression. **G.** Expression of BRAF V600E was weak but present, consistent with persistence of the mutation. Because the skull was decalcified, molecular confirmation was not possible.

Literature Review Summary

- Langerhans cells are specialized dendritic cells which present antigen to naïve T cells and are predominantly found in the epidermis.
- Langerhans cell histiocytosis (LCH) is a hematologic disease process where Langerhans cells proliferate as a localized or disseminated disease process.
- The disease is characterized by Birbeck (tennis racket) granules on electron microscopy as well as CD1a and S-100 positive by immunohistochemistry.
- It most commonly occurs in children under 15 years of age with a slight bias towards males with reported sex biases 1.6:1 (male: female).
- Langerhans Cell Histiocytosis has an incidence rate of 4.5 per million children. Among children, 63% of LCH neoplasms arise from bone or bone marrow.
- The single system Langerhans Cell Histiocytosis is the most prevalent type in children, accounting for 56-85% of all LCH recorded cases, sources provide statistics that multiple bone lesions occur approximately 19% of the time.
- The recurrence rate is relatively low, with a 5.7% recurrence in the unifocal bone disease, 12.5% reactivation in single system bone disease and 23.8% recurrence in multifocal bone disease.

Conclusions

- LCH can present in the skull as a localized lesion or as part of a disseminated disease process.
- The recurrence rate after treatment varies from 5.7% recurrence in unifocal bone disease, 12.5% reactivation in single system bone disease, and 23.8% recurrence in multifocal bone disease.
- When disseminated, with involvement of bone marrow, liver, or spleen, treatment is more challenging and survival is reduced.
- This case illustrates the challenges of effective treatment of LCH, particularly when disseminated, and the need for vigilant follow-up.

References

1. Allen CE, Merad M, McClain KL. Langerhans-Cell Histiocytosis. N Engl J Med. 2018 Aug 30;379(9):856-868.
2. Lin TE, Chu YY, Chang TY, Liao HT. Craniofacial involvement in Langerhans cell histiocytosis: A review of 44 cases at a single medical center. J Plast Reconstr Aesthet Surg. 2023 Jul;82:12-20.
3. Liu, H., Stiller, C. A., Crooks, C. J., Rous, B., Bythell, M., Broggio, J., Rankin, J., Nanduri, V., Lanyon, P., Card, T. R., Ban, L., Elliss-Brookes, L., Broughan, J. M., Paley, L., Wong, K., Bacon, A., Bishton, M., & West, J. (2022). Incidence, prevalence and survival in patients with Langerhans cell histiocytosis: A national registry study from England, 2013–2019. *British Journal of Haematology*, *199*(5), 728-738.
4. McClain KL, Bigenwald C, Collin M, Haroche J, Marsh RA, Merad M, Picarsic J, Ribeiro KB, Allen CE. Histiocytic disorders. Nat Rev Dis Primers. 2021 Oct 7;7(1):73.
5. Su M, Gao YJ, Pan C, Chen J, Tang JY. Outcome of children with Langerhans cell histiocytosis and single-system involvement: A retrospective study at a single center in Shanghai, China. Pediatr Hematol Oncol. 2018 Oct-Nov;35(7-8):385-392.
6. Titgemeyer C, Grois N, Minkov M, Flucher-Wolfram B, Gatterer-Menz I, Gadner H. Pattern and course of single-system disease in Langerhans cell histiocytosis data from the DAL-HX 83- and 90-study. Med Pediatr Oncol. 2001 Aug;37(2):108-14.