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CASE REPORT

Eosinophilic granuloma of the calvarium: is conservative management a valid option? Illustrative case and systematic review of the literature

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Abstract

Introduction Eosinophilic granuloma (EG) is the most common form of Langerhans cell histiocytosis, presenting as a single osteolytic lesion of the calvarium. Its diagnosis is based on typical clinical and radiological features. While surgical resection has been the standard treatment for EG, growing evidence favors watchful waiting, as unifocal calvarial lesions appear to frequently undergo spontaneous remission. However, histopathological confirmations of this hypothesis are still very limited.
Methods Methods. Here, we report a case of EG with typical clinical and radiological features which, due to intervening circumstances, was resected in a delayed fashion. Moreover, we perform a systematic review of the literature on conservative management of EG.
Results In our case, histological examination showed ongoing bone regeneration with no traces of the disease. Through our literature review, we found 47 cases of calvarial EG managed with watchful waiting. No active intervention was required in 43 cases (91%). Four patients (9%) received surgery or chemotherapy due to the persistence/progression of symptoms or family request. Three reports other than ours documented spontaneous disease remission in surgically resected EG upon histopathological examination.
Conclusion Our report provides further evidence that watchful waiting can be a reasonable option in the management of single calvarial EG.

Keywords Eosinophilic granuloma · Histiocytosis · Skull · Conservative · Observation · Review

Introduction

Eosinophilic granuloma (EG) is a disease in the spectrum of Langerhans cell histiocytosis (or histiocytosis X), usually developing as a single focal osteolytic lesion affecting children or young adults. Though the overall incidence in the general population is low (1–5 cases per million each year) [1], EG is not uncommon to encounter in neurosurgical practice *since the most frequently affected skeletal district is the calvarium*. Multiple cases have been reported in a series of pediatric calvarial masses [2, 3]. Usually, EG is treated with supramarginal resection of the affected bone and cranioplasty; nonetheless, a new trend towards conservative management has emerged over recent years as reports of spontaneous remission have started to increase [4–6].

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We report the case of a patient with the typical clinical and radiological presentation of EG showing radiological and pathological evidence of spontaneous remission at the time of surgery. We subsequently perform a systematic literature review about spontaneous remission of EG.

Case description

A 20-year-old male presented with a tender lump in the left parietal region. A head CT scan showed a solitary 2-cm punched-out lytic lesion of the left parietal calvarium with scattered calcifications and reactive swelling of the overlying soft tissues, consistent with EG (Fig. 1). A subsequent MRI scan confirmed the diagnostic hypothesis, displaying a slight increase in the size of the lesion (Fig. 1). We hence performed a skeletal survey which excluded the presence of any further lytic areas other than the growing EG of the calvarium. We discussed the radiological progression with the patient and offered surgery, which was delayed upon his request due to both personal reasons and the ongoing COVID-19 pandemic.

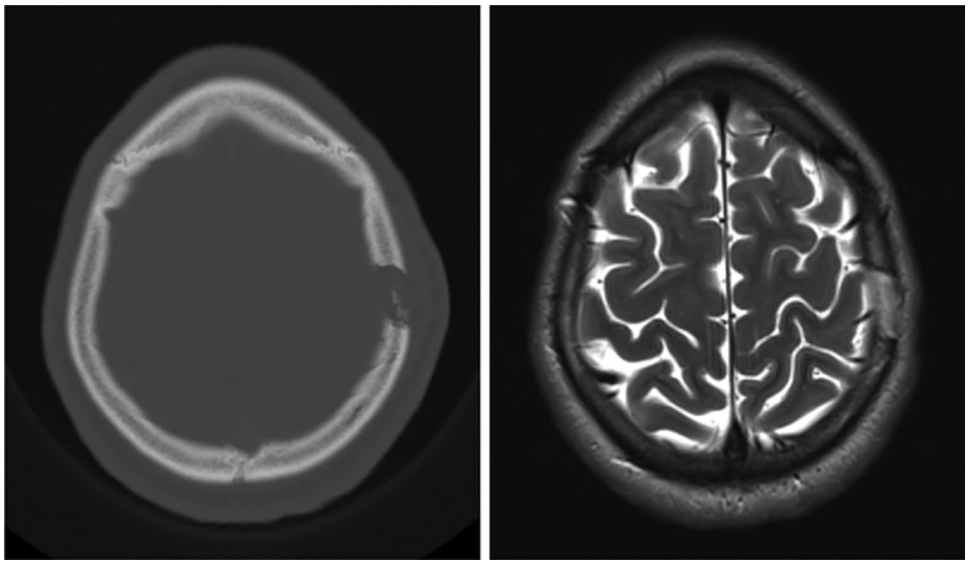

Fig. 1 CT (left) and MRI (right) scans of the patient at initial diagnosis. The CT scan shows the typical appearance of EG, with asymmetrical involvement of the outer and inner table of the calvarium and the sequestered calcifications. T2 MRI sequences, performed when the scalp swelling had already subsided, show bone marrow edema

In the meanwhile, swelling and pain gradually subsided, eventually being replaced by a palpable hollowing in the skull. At the time of surgery (9 months from initial presentation), a preoperative head-CT scan showed partial bone healing (Fig. 2). Due to the persistent palpable bone defect of the left parietal region and the patient's motivation, we resected the lesion.

We performed a circumferential craniectomy with subsequent reconstruction with bone cement and titanium miniplates (Fig. 2).

Pathologic examination of the resected tissue showed bone necrosis and fibrosis with perivascular mononuclear cells; though features were suggestive of ongoing bone remodeling and repair (Fig. 3), staining for S100, CD1a, and Langerin did not show histiocytes infiltrating the specimen.

Methods

Two authors (A.B. and F.R.) reviewed independently all the published cases of EG of the calvarium in the PubMed database by using the following research quote: ("eosinophilic granuloma" OR "langerhans cell histiocytosis") AND ("skull" OR "calvarium"). The review was conducted systematically by following the PRISMA guidelines [7] (Fig. 4).

Results

We identified 47 cases of calvarial EG managed expectantly (Table 1). Most data came from retrospective studies; however, 17 cases were part of a recent international prospective study [8]. All reports involved children, adolescents, or young adults

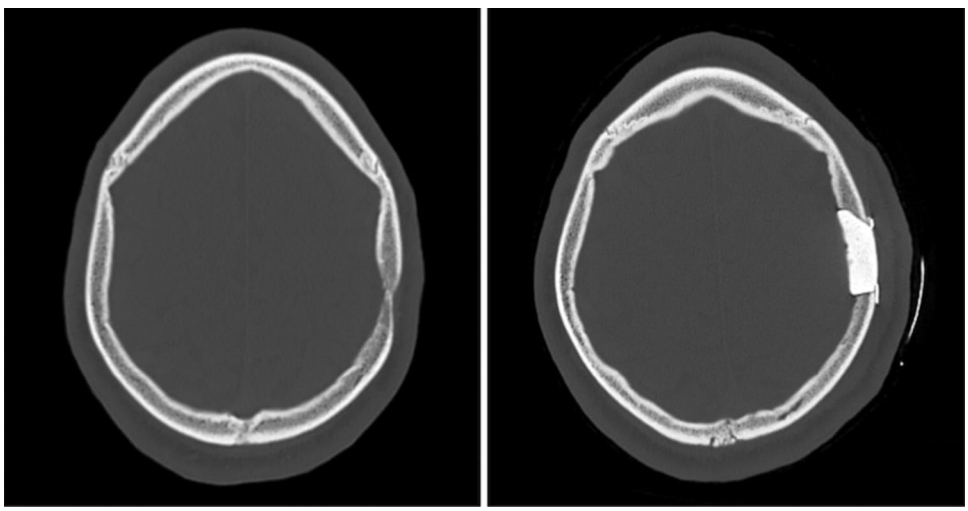

Fig. 2 Immediate preoperative CT scan (left, showing partial bone healing) and postoperative CT scan (right, showing resection of the defect and reconstruction with bone cement and titanium miniplates)

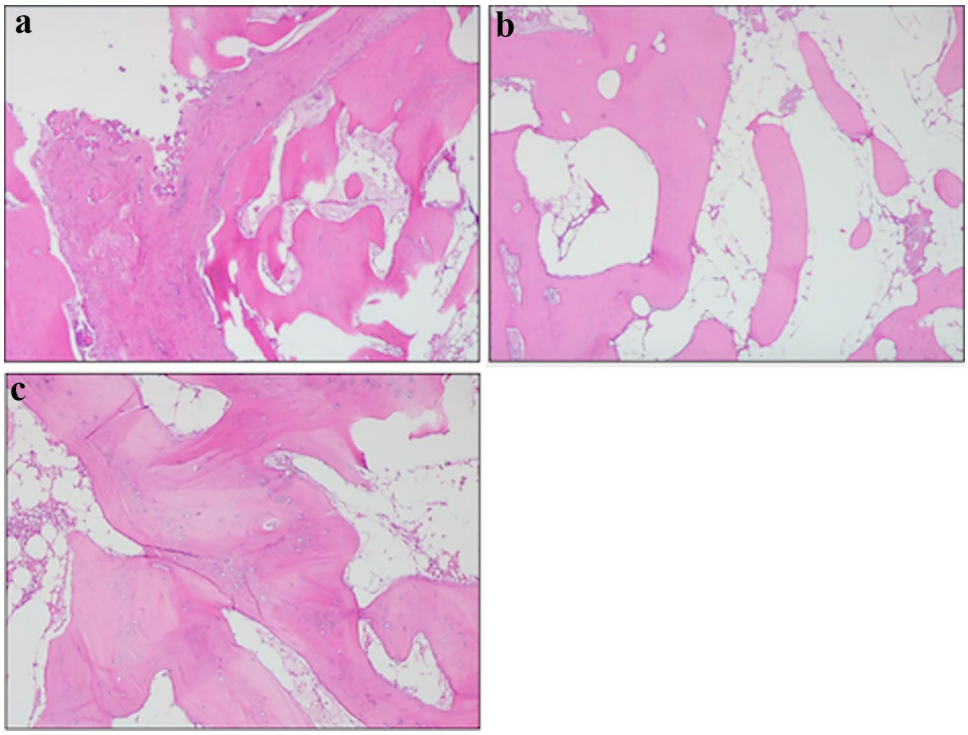

Fig. 3 Pathological specimens after E&E staining show bone trabeculae with partially necrotic remodeling aspects and associated adipose replacement of the bone marrow spaces (**a**, 5×) and irregular thickening of the bony trabeculae with remodeling (**b**, 5×). Marked thickening and irregularity of the bony trabeculae with aspects of new osteoid matrix deposition and bone remodeling can be seen in **c** (10×). The impression from the pathological examination is suggestive of a reactive osteo-reparative phenomenon to a pathological process that is no longer present

with no patients being older than 22 and most patients being under 10. All patients harbored a single osteolytic lesion of the calvarium with typical clinical and radiological features of EG. In all cases, a skeletal survey was performed to rule out multifocal disease. Some authors adopted further exclusion criteria, such as the presence of signs of systemic inflammation [9]. Mean follow-up ranged from 12 to 77 months.

In 43 cases (91%), no active intervention was required, and spontaneous clinical remission was evident. Data from follow-up imaging were available for 28 of these patients, showing complete radiological remission in 24 (86%) and partial remission in 4 (14%). In the latter 4 cases, the last available radiological assessment was at 5–12 months from the onset of symptoms.

Among patients failing conservative management, 2 received chemotherapy due to symptomatic progression in a few weeks [9], one was surgically treated due to persistent pain at 2 months [5], and one ultimately underwent surgery at family's request [8].

Discussion

Unifocal involvement of the skull is the most common single-site presentation of eosinophilic granuloma, considered the mildest form in the spectrum of Langerhans cell histiocytosis [13]. The rarity of this pathology has been an obstacle towards the development of univocal treatment guidelines [5]. Surgical treatment of isolated calvarial EG has been and diffusely continues to be standard practice [5, 13]. However, following the first report of 4 patients exhibiting spontaneous resolution of EG by Oliveira and colleagues [6], there has been growing evidence that calvarial EG can be managed expectantly with clinical and radiological follow-up (Table 1) [4–6, 8, 13].

The pathophysiology underlying spontaneous remission of EG has not been studied extensively, though it is likely that there are multiple factors involved. In inflammatory-related lesions such as eosinophilic granuloma, cessation of inflammation may be the mechanism of growth arrest and the subsequent remission characterized by the replacement of necrotic tissues. However, it seems that mechanisms of excessive immune tolerance (via local expansion of T-regulatory lymphocytes) play a pivotal role in allowing localized survival of clonal histiocytes, which would otherwise be eliminated by the immune system [14]. It is thus reasonable to hypothesize that spontaneous disease remission occurs due to loss of tolerance, facilitating the aggression of clonal histiocytes by an immune reaction [6]. It has been demonstrated that low-risk and high-risk manifestations of the disease have different molecular and histopathological features [9]; this could be the reason why spontaneous remission has been observed mainly in low-risk cases of unifocal bone involvement.

Womer et al. [15] demonstrated the natural history of the spontaneous regression in some cases of histiocytosis X. They reported 42 patients with a mean age of 5.3 years harboring bony lesions and showed that median time to a given

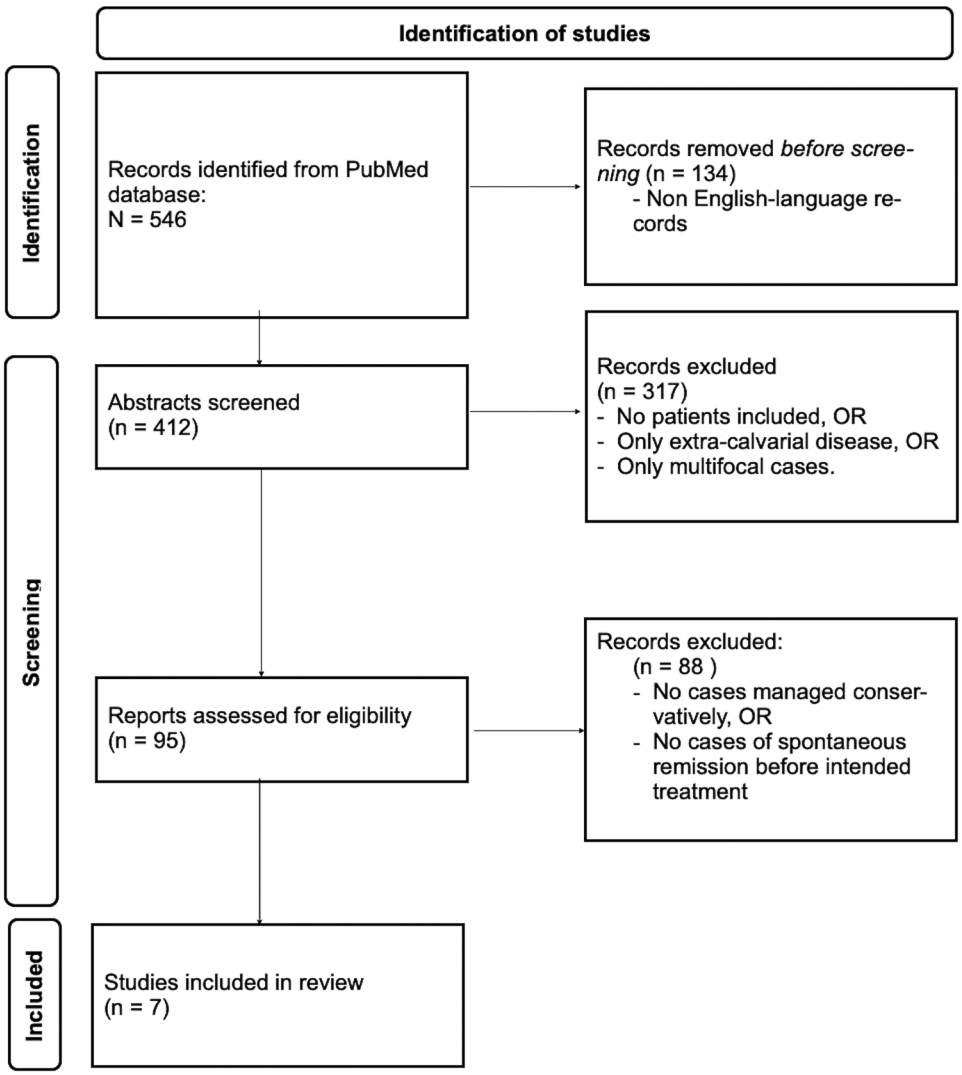

Fig. 4 PRISMA workflow for our systematic literature review [7]

degree of healing was similar between treated and untreated lesions. After careful examination of the time course of healing, it was demonstrated that some degree of repair should be apparent 4 months after diagnosis, yet complete healing may take many months.

Clearly, in all of the cases summarized in Table 1, no histopathological confirmation of disease remission was available, and quiescent disease could not be completely ruled out [8]. Aside from our report, there are three previous cases in literature of calvarial EG resected during or after healing with histology confirming disease remission [4, 16]; pathology findings were similar to our case's observations [16]. Interestingly, in one of these cases, histological findings (ongoing bone regeneration with granulation tissue and fibrosis) prompted the authors to believe that the lesion was indeed a growing skull fracture, mistaken for EG. However, in view of the aforementioned data, the hypothesis of a healing EG appears indeed consistent and compelling [16, 17].

Conservative management of calvarial EG is favored by several elements:

- The characteristic clinical and radiological features of EG, that allow to formulate a sufficiently solid diagnosis even in the absence of biopsy confirmation (see below).

- The low risk of recurrence or diffusion to other organs (contrary to the skull base and orbital lesions, calvarial EG is not associated with the risk of CNS involvement [18]).

- The typically mild nature of the associated symptoms and their limited duration.

- The accessibility of the lesions for monitoring with both clinical examination and, potentially, easily available diagnostic modalities, such as ultrasound [11, 13] which *has been proposed as a valid follow-up imaging modality, with the advantage of sparing young patients from radiation* [11].

In the majority of studies, the diagnosis was based on CT scans combined with a typical clinical presentation, that are pathognomonic [3, 13, 19]. In particular, head CT

Table 1 Summary of the published cases of EG managed with observation only

Source	Study type	N. of patients	Age (mean)	Mean follow-up (range)	Diagnostic modality	Mean time to remission (range)	Radiological remission* at last FU	No. undergoing treatment, reason (%)
Oliveira 2003 [6]	Retrospective cohort	4	8 years	34 (3–82) months	CT (75%), X-ray (25%)	6 (3.5–8) months	Complete (25%), partial (25%), NA (50%)	0 (0%)
Conforti 2010 [10]	Case report	1	16 years	48 months	CT, MRI	NR	Complete	0 (0%)
De Angulo 2013 [5]	Retrospective cohort	8	10 years	12 (7–19) months	CT (76%), CT and MRI (12%), X-ray (12%)	12 months (improvement at 3 months)	Complete (75%, partial (25%)	1 (12%) underwent surgery for persistent pain & enlargement at 2 months
Vanhoenacker 2018 [11]	Case report	1	8 years	20 months	CT, MRI, ultrasound	14 months	Complete	0 (0%)
Oh 2020 [9]	Retrospective cohort	15	< 10 years	62 months	Biopsy (30%), NR (70%)	NR	NR	2 (13%) underwent chemotherapy due to local progression (pain and swelling)
Pires 2021 [12]	Case report	1	18 years	12 months	CT, MRI, X-ray	6 months	Incomplete	0 (0%)
Steinbok 2022 [8]	Prospective international study	17	< 22 years	77 (32–118) months	CT and X-ray (100%)	12 months (improvement at 2 months)	Complete (88%), NA (12%)	1 (6%) underwent surgery at family's request at 2 months

NA Not assessed or lost to follow-up

*Remission is defined as disappearance of symptoms AND of any palpable anomaly of the skull

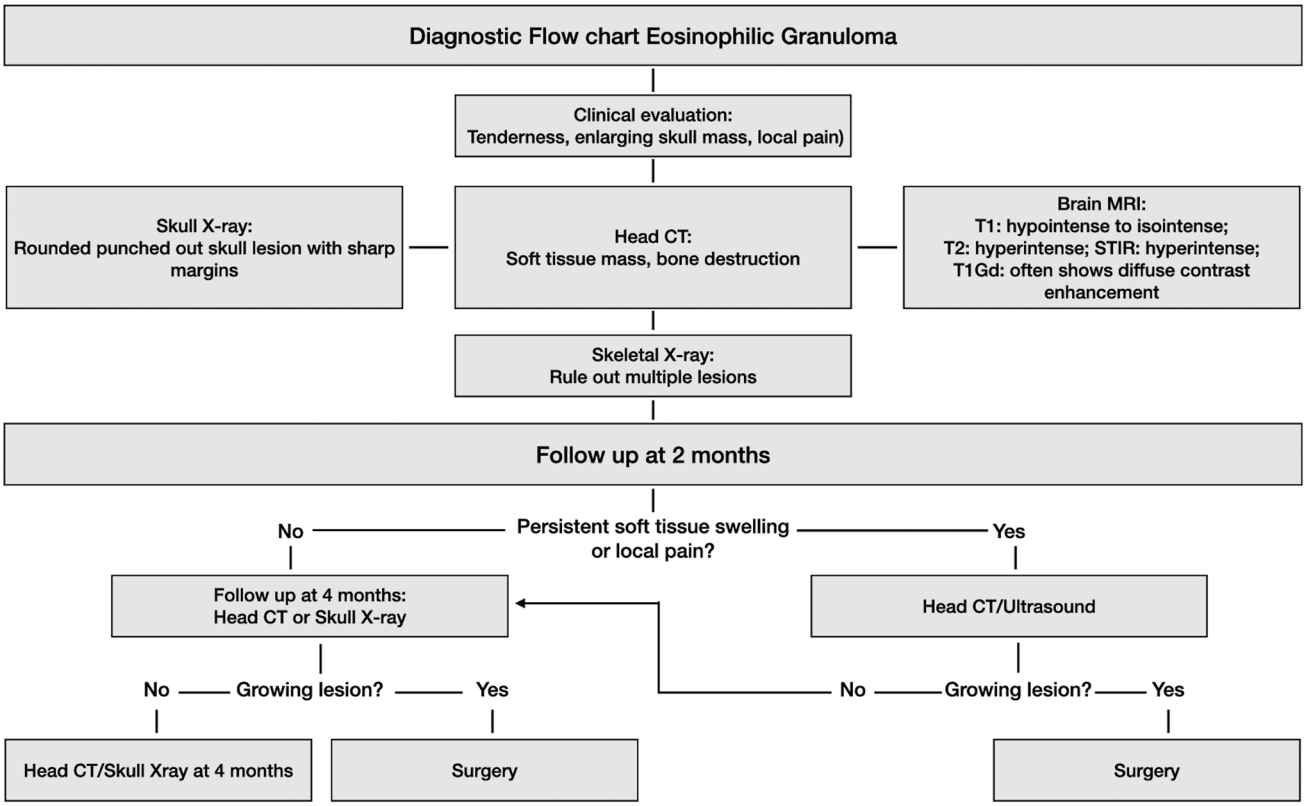

Fig. 5 An example of an algorithm for diagnosis and management of unifocal calvarial EG

shows a circular area of osteolysis with unequal involvement of the outer and inner table and no sclerotic rims [3, 19] (Fig. 1). Swelling of the overlying soft tissue layers is usually associated. "Sequestered" calcifications may be evident, representing islands of bone engulfed by the disease [19] (Fig. 1). MRI appearance is heterogeneous, but generally characterized by extensive bone marrow edema (Fig. 1) and strong contrast enhancement; reactive dural enhancement may also be present [19] (Fig. 5).

It is worth mentioning that in the literature, there are cases of unifocal disease showing recurrence or progression [4, 13]. In their systematic review of published case series, Bezdjian and colleagues [13] hypothesize that these may have been multifocal forms that were missed at first due to the lack of systemic investigations, highlighting the importance of performing a skeletal survey as part of the initial workup. Some authors have reported cases of recurrence or progression even in cases that were proven as unifocal at initial radiological assessment; however, they do not report the initial disease location [4] (it is well established that the behavior of calvarial lesions is different from that of EG occurring in other cranial and extra-cranial bones [18]). In summary, we believe that current data are too fragmentary and do not allow to draw any conclusion against conservative management for EG.

As a closing remark, we care to point out that almost all data in the literature concern children and young adults. Observation of suspicious calvarial EG in older adults is less favored due to the increasingly higher probability of alternative diagnoses, such as metastasis.

Conclusions

Though surgical excision remains the standard treatment for single-lesion calvarium EG, there is growing evidence that such lesions may heal spontaneously with conservative management. Close follow-up and a conservative strategy may be an option when typical symptoms are in remission.

Author contribution A. B. and F. R. wrote the manuscript text, performed the literature search, and prepared Figs. 1, 2, 4, 5, and Table 1. G.R. contributed to the manuscript and prepared Fig. 3. All authors reviewed the manuscript.

Data availability All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate No ethics approval was necessary for this study (case report and review of the literature). Written

informed consent was obtained from the patient for the publication of this case report and accompanying images.

Conflict of interest The authors declare no competing financial or non-financial interests. There are no conflicts of interest.

References

1. Hu X, Buhtoiarov IN, Wang C, Sun Z, Zhu Q, Huang W, Yan W, Sun Y (2022) Langerhans cell histiocytosis: a population-based study of anatomical distribution and treatment patterns. J Bone Oncol 36:100454
2. Gibson SE, Prayson RA (2007) Primary skull lesions in the pediatric population: a 25-year experience. Arch Pathol Lab Med 131(5):761–766
3. Yoon SH, Park S-H (2008) A study of 77 cases of surgically excised scalp and skull masses in pediatric patients. Childs Nerv Syst 24(4):459–465
4. Davidson L, McComb JG, Bowen I, Krieger MD (2008) Craniospinal Langerhans cell histiocytosis in children: 30 years' experience at a single institution. J Neurosurg Pediatr 1(3):187–195
5. De Angulo G, Nair S, Lee V, Khatib Z, Ragheb J, Sandberg DI (2013) Nonoperative management of solitary eosinophilic granulomas of the calvaria: Clinical article. J Neurosurg Pediatr 12(1):1–5
6. Oliveira M, Steinbok P, Wu J, Heran N, Cochrane D (2003) Spontaneous resolution of calvarial eosinophilic granuloma in children. Pediatr Neurosurg 38(5):247–252
7. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372:n71
8. Steinbok P, Cheong A, Dix DB et al (2022) Nonoperative management of childhood calvarial Langerhans cell histiocytosis. N Engl J Med 386(26):2532–2534
9. Oh B, Lee S, Ke Y, Kimpo M, Yeoh A, Quah TC (2020) A "Wait-and-See" approach to quiescent single-system Langerhans cell histiocytosis to spare children from chemotherapy. Front Pediatr 8:466
10. Conforti R, Porto A, Cirillo M, Sgambato A, Galderisi S, Cirillo S (2010) Spontaneous resolution of eosinophilic granuloma in a patient with a psychotic disorder. Neuroradiol J 23(4):437–442
11. Vanhoenacker F, Verlooy J, De Praeter M (2018) Spontaneous resolution of unifocal Langerhans cell histiocytosis of the skull: potential role of ultrasound in detection and imaging follow-up. J Ultrason 18(74):265–270
12. Pires T, Duarte Santos C, Gonzalez Santos M, Luz L, Ferrão A, Banza MJ (2021) Eosinophilic granuloma: a rare and often benign condition presenting as a lump on the head, which was easily treated. Eur J Case Rep Intern Med 11
13. Bezdjian A, Alarfaj AA, Varma N, Daniel SJ (2015) Isolated Langerhans cell histiocytosis bone lesion in pediatric patients: systematic review and treatment algorithm. Otolaryngol Neck Surg 153(5):751–757
14. Senechal B, Elain G, Jeziorski E, Grondin V, Patey-Mariaud de Serre N, Jaubert F, Beldjord K, Lellouch A, Glorion C, Zerah M, Mary P, Barkaoui M, Emile JF, Boccon-Gibod L, Josset P, Debré M, Fischer A, Donadieu J, Geissmann F. Expansion of regulatory T cells in patients with Langerhans cell histiocytosis. PLoS Med. 2007 Aug;4(8):e253
15. Womer RB, Raney RB Jr, D'Angio GJ (1985) Healing rates of treated and untreated bone lesions in histiocytosis X. Pediatrics 76(2):286–288
16. Hollon T, McKeever PE, Garton HJL, Maher CO (2015) Skull fracture mimicking eosinophilic granuloma. Childs Nerv Syst 31(7):1171–1174
17. Steinbok P (2015) Healing calvarial eosinophilic granuloma or healing skull fracture? Childs Nerv Syst 31(7):1175–1176
18. Haupt R, Minkov M, Astigarraga I et al (2013) Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years: Guidelines for Langerhans Cell Histiocytosis. Pediatr Blood Cancer 60(2):175–184
19. Gomez CK, Schiffman SR, Bhatt AA (2018) Radiological review of skull lesions. Insights Imaging 9(5):857–882

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