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Rare Onset of Erdheim-Chester Disease in Children and Young Adults: A Case Series and Review of the Literature

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Established Facts

- Rare cases of Erdheim-Chester disease in the pediatric and young adult populations.

Novel Insights

- Two new cases of Erdheim-Chester disease with singular clinical presentation and review of the literature.

Keywords
Pediatric neurosurgery · Pediatric population · Central nervous system

Abstract
Introduction: Erdheim-Chester disease (ECD) is a rare histiocytic neoplasm that affects patients, predominantly males aged 40–70 years, with very heterogeneous clinical presentation and prognosis. In 2020, Goyal et al. proposed consensus recommendations for the management of patients with ECD, remarking on the exceptional

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presentation of the disease in the pediatric population. ***Case Presentation:*** The first patient, a 20-year-old male, underwent cervical laminectomy and partial removal of a cervical spine lesion, initially apparently consistent with cervical schwannomas. The second patient, a 9-year-old female, received surgery for an extra-axial lesion of the greater sphenoid wing, radiologically consistent with a meningioma. ***Conclusion:*** At present, 15 pediatric cases have been reported in the literature with involvement of the central nervous system, with no consensus on the diagnostic and therapeutic management, as Pegoraro et al. evidenced in their pediatric multicenter case series. The present article adds two new cases of ECD with onset in childhood and young adulthood, who received the diagnosis after neurosurgical procedures.

Introduction

Erdheim-Chester disease (ECD) is a rare multisystem disease, classified by the WHO as a neoplasm of the myeloid lineage with chronic and uncontrolled inflammation [1]. Histiocyte infiltration induces fibrosis in affected tissues, leading to organ failures in some cases. In some patients, ECD has an indolent course, while in others may affect multiple organs, including the central nervous system (CNS), long bones, retroperitoneum, heart, large vessels, and lungs [2, 3].

ECD typically affects adults in the sixth decade of life and is exceptional in children [4–14]. Herein, we report two cases of juvenile ECD with CNS involvement that have required neurosurgical management.

Case Series

Case 1

The first patient is a 20-year-old male who showed good clinical conditions, except for thrombocythemia, until 16 years of age. His family history was positive for rheumatological diseases as his brother was affected by sacroiliitis and spondyloarthritis (in treatment with nonsteroidal anti-inflammatory drugs). In October 2019, at 17 years of age, he started complaining of migrating pain along legs and arms, followed by persistent diplopia 2 months later. Magnetic resonance imaging (MRI) of the brain revealed the presence of a brain tumor of the pineal region, which was biopsied in March 2020. Histological evaluation was consistent with pilocytic astrocytoma (Fig. 1).

The migrating pains regressed along with the steroid treatment but abruptly reemerged after the medical therapy was stopped, with more severe symptoms affecting the joints of the ankles, knees, and wrists. Further rheumatological investigations documented the presence of active spondyloarthritis with axial and peripheral involvement. Muscle biopsy and electromyography studies evidenced axonal sensitive polyneuropathy and iatrogenic myopathy, secondary to glucocorticoids. The bone density scan documented osteopenia (glucocorticoid-related), which was treated with oral vitamin D. Following the development of thrombocytopenia and the persistence of migrating pains, the patient underwent a bone marrow biopsy, which did not show any abnormalities.

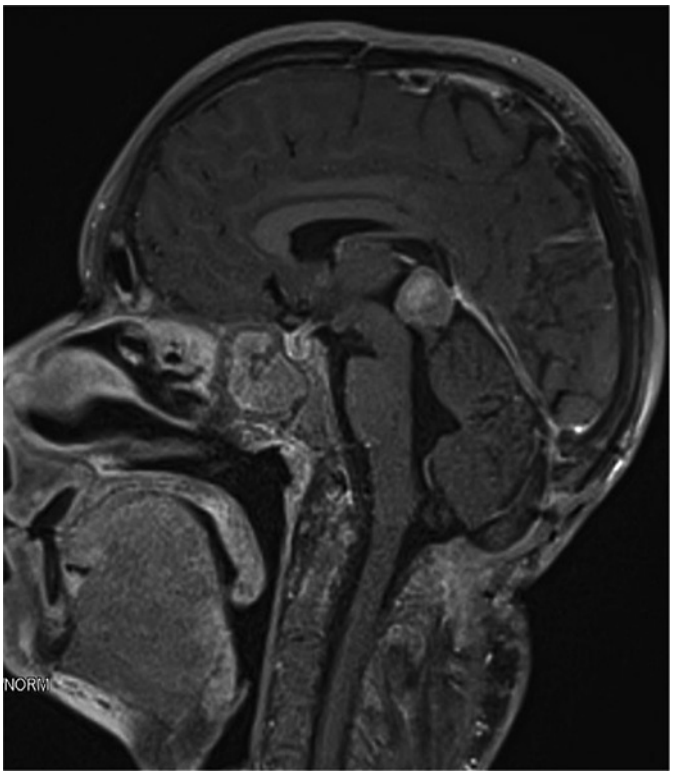

Fig. 1. Sagittal T1 post-contrast MRI scan showing a neoplasm of the pineal region. Histological evaluation was consistent with pilocytic astrocytoma.

The migrating pain started to get worse from the beginning of 2022, especially affecting the right side of the body. A whole-body (WB) positron emission tomography (PET) scan was performed in April 2022, which showed a highly metabolic disease. Of note, FDG uptake was detected in the pineal gland, which was not consistent with the previous diagnosis of pilocytic astrocytoma. Therefore, an MRI of the brain and the spine was performed, which excluded the growth of the pineal gland neoplasm. However, a thickening of the cervical nerve roots (left-sided on C1 and bilateral from C5 to D1) was detected, involving the intradural components and showing areas of nodular impregnation that marked the medullary cord (Fig. 2). These findings were consistent with bilateral schwannomas. Therefore, a surgical procedure was recommended, aiming to decompress the spinal cord and get the histology of the lesions. The patient underwent a C6-C7 laminectomy and a subtotal exeresis of the lesions. The post-operatory course was unremarkable, except for left-arm hypoesthesia, and the myeloid-radicular pain progressively decreased. The

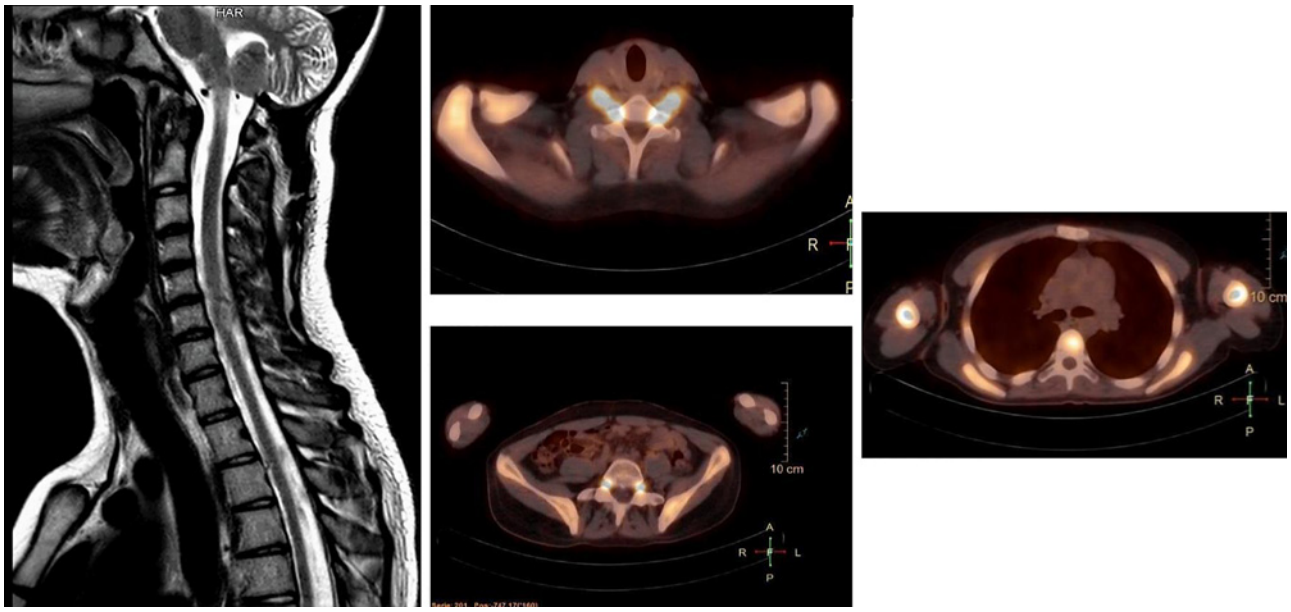

Fig. 2. Sagittal T2 MRI scan showing areas of nodular impregnation that marked the cervical medullary cord, especially at the level of the 6th cervical vertebra and a WB PET-FDG showing a highly metabolic systemic disease. Histopathology: ECD disease.

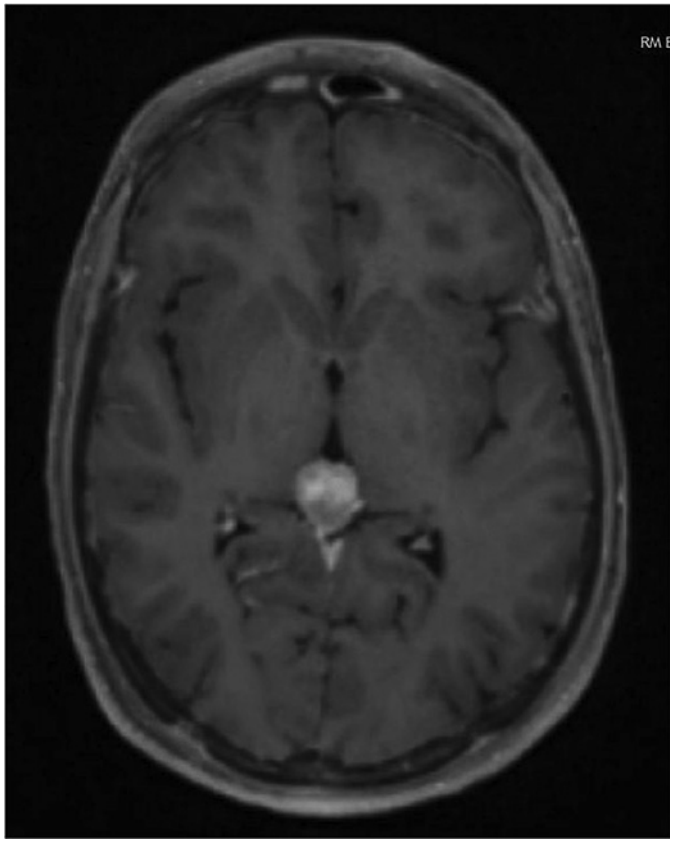

Fig. 3. Axial T1 post-contrast brain MRI scan documenting a slight reduction in the size of the pineal lesion.

histological evaluation revealed ECD (CD68+, CD14+, S100−, CD1a−, CD207− histiocytic infiltrate; BRAFV600E−; no emperipolesis). Considering the diffused bone involvement shown in the PET scan, a bone marrow biopsy was performed, with evidence of infiltration by histiocytes with the abovementioned immunohistochemical features. Therefore, considering the systemic involvement of the disease, the patient received everolimus (7 mg/die), with significant improvement in his clinical condition. Interestingly, the last brain MRI scan (Fig. 3) documented a slight reduction in the size of the pineal lesion, which confirmed the first histology wrong, probably due to its mistargeting during surgery.

Case 2

The second patient is a 9-year-old girl who was diagnosed with hemophagocytic lymphohistiocytosis in 2017 at the age of 4 years, after the appearance of recurrent otitis, left otomastoiditis, persistent fever, anemia, and thrombocytopenia. In March 2018, she was evaluated for diabetes insipidus and growth hormone (GH) deficiency and received hormone replacement therapy with desmopressin (Minirin/dDAVP, 15 mg in the morning and afternoon and 30 mg at evening) and GH (Humatrope/Somatropine 12 mg 0.55 UI once a day). Brain MRI showed thickening of the pituitary stalk and multiple lesions involving the left periorbital space and the left infratemporal fossa. A biopsy of the periorbital mass and a concomitant bone marrow biopsy were consistent with LCH (CD1a+, BRAFV600E+). The patient received chemotherapy according to the LCH-IV protocol (stratum I) and desmopressin for central diabetes insipidus and initially responded to therapy. However, in September 2019, the patient presented an asymptomatic multisystemic LCH reactivation and consequently received a second-line chemotherapy treatment (LCH IV, stratum II) to achieve disease stabilization. In a follow-up WB MRI performed in August 2019, a sleeve epidural lesion with contrast uptake appeared at the cone-cauda level (Fig. 4). Considering

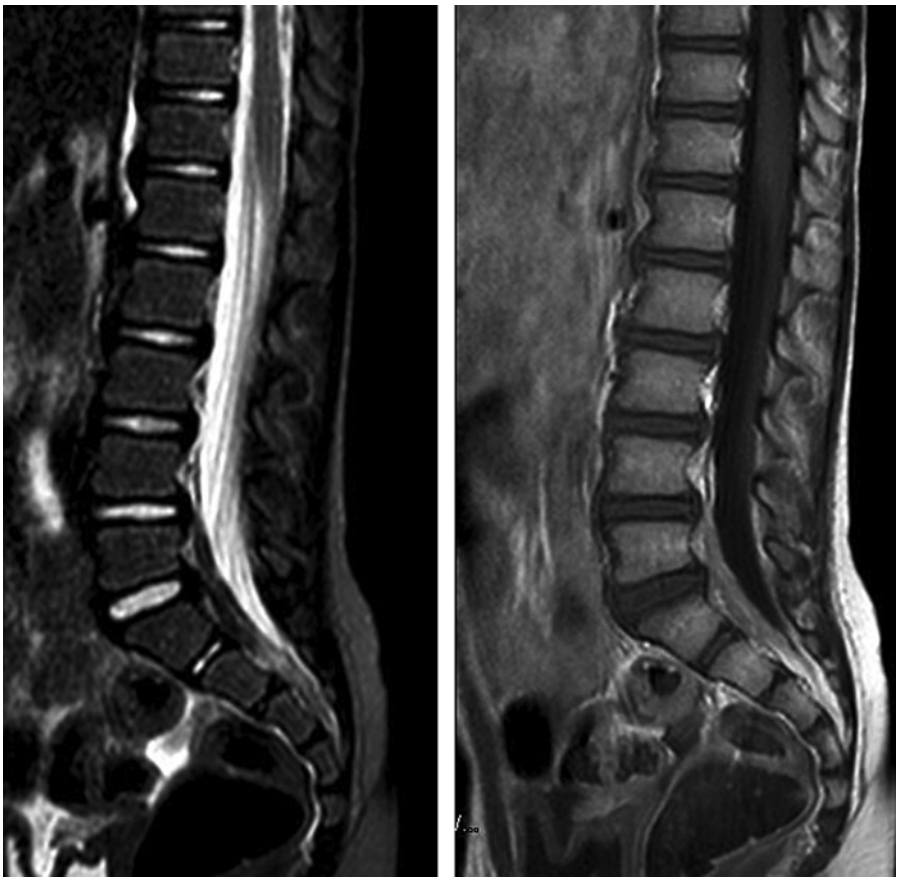

Fig. 4. Sagittal T2 and T1 MRI scan with a sleeve epidural lesion at the cone-cauda level.

the persistence of the lesion over the follow-up evaluations and its localization, atypical for LCH, in November 2020, the patient underwent an S4-S5 laminectomy and a lesion biopsy. On histological examination, a fibro-adipose tissue with inflammatory infiltrated rich in macrophages (CD68+) was found, while all LCH markers proved negative. In April 2022, a follow-up WB-MRI detected an intracranial extra-axial lesion with dural implantation on the left greater sphenoid wing, i.e., planum temporalis, the site where faded extra-axial enhancement was previously shown (Fig. 5). Therefore, in May 2022, the patient received a left frontotemporal craniotomy with radical resection of the lesion (Fig. 6). The post-operatory course was normal. The histological evaluation showed ECD (CD68+, CD14+, FXIII+, CD1a−, S100−, BRAFV600E+). Considering the slow disease progression, treatment with pegylated alpha interferon (90 μg, once a week) was introduced. At the last follow-up, no signs of active disease were found. Therefore, she currently continues her treatment with pegylated alpha.

Discussion

The present report provides two new cases of ECD undergoing neurosurgical procedures. Less than 1,000 cases of ECD are reported in the literature, the majority of them diagnosed with ages between 40 and 70 years, and approximately 60% affects men [2, 3, 15].

The most frequent causes of death in patients with ECD derive from respiratory distress, pulmonary fibrosis, and heart failure. Blood count abnormalities are frequent, with anemia and a high neutrophil count, usually secondary to systemic inflammation. These findings were observed in both our patient cases. According to Cives et al. [3], cerebellar and pyramidal syndromes are some of the most frequent neurological signs in ECD patients. Other described features included not only seizures, headaches, neuropsychiatric signs or cognitive impairment, sensory disturbances, and cranial nerve paralysis but also exophthalmos, gaze disturbances, diabetes insipidus, and focal mass lesion-related radiculopathies [3]. CNS lesions are directly responsible for one-third of all deaths. In their cohort of patients, diabetes insipidus was associated with the thickening of the pituitary stalk and alteration of the brightness of the hypophysis or pituitary infiltration in 12%, 6%, and 3% of patients, respectively [3]. In a systematic literature review of ECD cases with

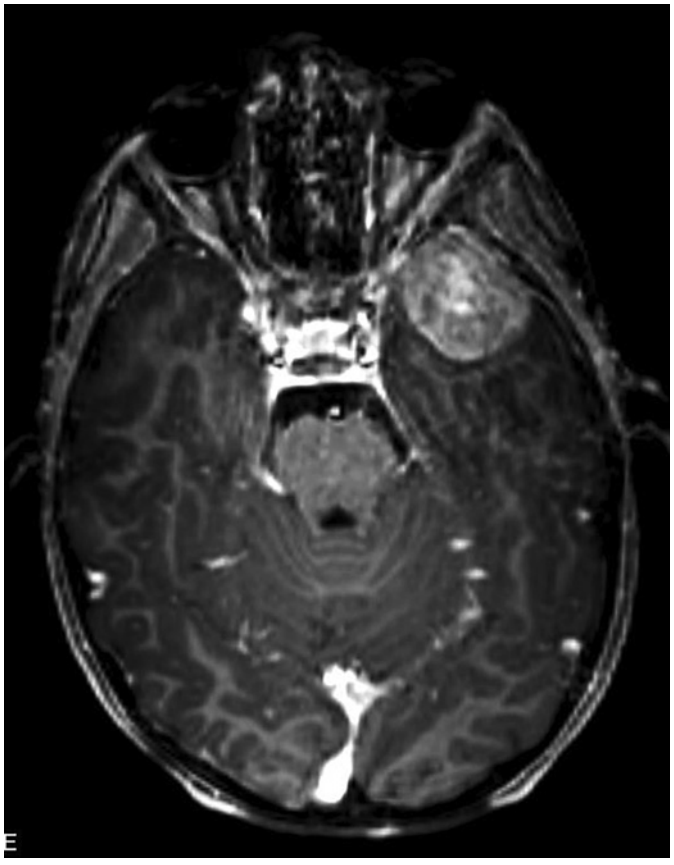

Fig. 5. Axial post-contrast MRI scan before surgery of removal of an intracranial extra-axial lesion with dural implantation located in the left temporo-polar region.

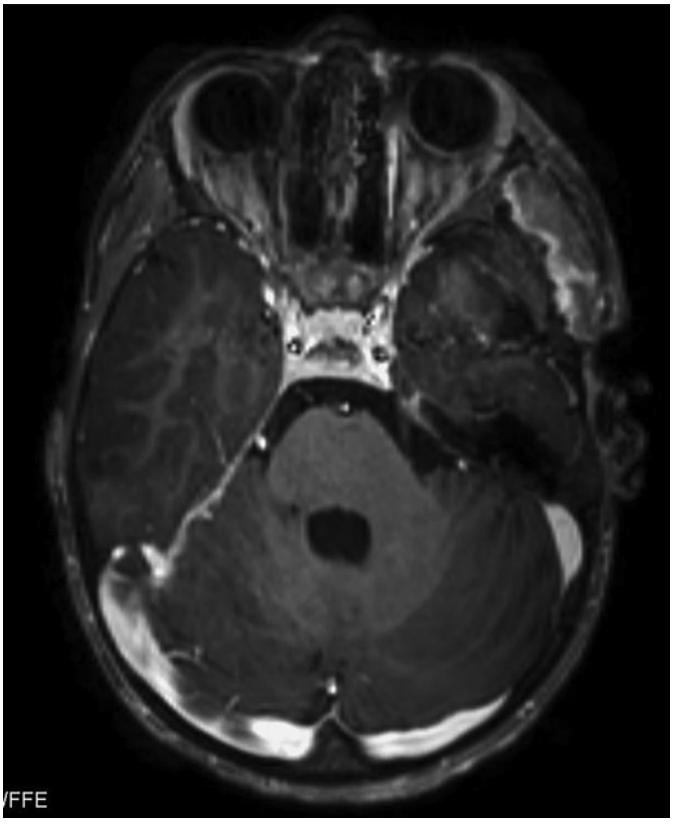

Fig. 6. Axial post-contrast MRI scan after surgery of removal of an intracranial extra-axial lesion with dural implantation located in the left temporo-polar region.

neurological involvement, Haque et al. [16] noticed that the most common neurological symptoms were cranial neuropathies and ataxia. Moreover, they noticed that 50% of patients had parenchymal lesions involving the cerebral hemispheres, pituitary gland, or hypothalamus; 35% had brainstem lesions, and 25% cerebellar involvement, 17.5% dural involvement, and 10% dural as well as parenchymal lesions were found on MRI. According to neuroradiological findings, Lachenal et al. [17] reported three different types of CNS involvement: an infiltrative pattern in 44% of cases, with widespread nodules or masses in the brainstem, cerebellum, and cerebral hemispheres; a meningeal pattern forming meningioma-like tumors or nodular thickening of the dura mater (37%); a composite pattern with both types of lesions (19%). The neurological examination of our first patient initially showed persistent diplopia, as well as diabetes insipidus and GH deficiency, which were observed also in our second patient. Concerning radiological findings, on MRI scan, the first patient presented with a thickening of the cervical nerve roots (left-sided on C1 and bilateral from C5 to D1) (Fig. 2), involving the intradural components and showing areas of nodular impregnation that marked the medullary cord; he also underwent a biopsy of a pineal region lesion previously, pilocytic astrocytoma on histology, finding being not completely compatible with PET FDG uptake of the pineal gland. The second patient showed an intracranial extra-axial lesion with dural implantation on the left greater sphenoid wing (Fig. 5). Histological ECD hallmarks include the presence of CD68-positive and CD1a-negative lipid-laden histiocytes with small nuclei, Touton-like multinucleated giant cells, scanty lymphocytic infiltrate, tissue eosinophilia, and marked fibrosis. In 2012, progress in molecular techniques led to the discovery of recurrent BRAFV600E mutation in histiocytes from ECD lesions [15, 18], and therapies targeting BRAF, such as vemurafenib, a specific BRAF inhibitor, were developed subsequently. Other

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Table 1. Clinical features of 15 reported pediatric patients with Erdheim-Chester disease and CNS involvement

Reference	No./ sex	Age of the onset	Extra-skeletal signs	Bone pain	Bone mass	Location	X-ray localization	CT scan	MRI	Type of histology sample	TT
Globerman et al. [13] (1991)	1/M	7	Neck mass, DI GH deficit	No	No	No	Typical (long bones, calvarium, skull)	Mediastinum kidney, retroperitoneal mass, sclerotic vertebrae ribs	Brain N	Bone, mediastinum	NR
Clerico et al. [10] (2003)	2/F	13	Omentum, breast, and lungs	Yes	Swelling	Knee, elbow	Typical (femur, tibiae, radius, humerus, ulnae, skull, vertebrae, ribs)	Femur, humerus, and tibia	Brain, thalamus, and bone	Bone, abdomen	CS CT
Nagatsuka et al. [11] (2005)	3/F	13	Brain	Yes	Yes	Jaw	Typical (tibiae, fibulae, and maxillae)	Bone, brain	Brain	Maxillae, mandibulae	NR
Joo et al. [12] (2005)	4/F	10	NR	Yes	Tenderness	Knee, elbow	Typical (upper and lower limbs, ulnae, and mandible)	NR	Typical (bone marrow)	Bone	CS
Ozdemir et al. [9] (2007)	5/M	4	DI, cerebellar syndrome, and sellar cavity mass	No	No	No	Typical (femurs)	NR	Typical (femur, sellar cavity mass)	Extra-axial mass	CS
Tran et al. [4] (2009)	6/F	7	Retroperitoneal infiltration, HSPM	Yes	No	Knee elbow	Typical (femur, tibiae, humerus, skull, rib, and pelvis)	Bone	Typical (retroperitoneum)	Bone	IFN-alpha
Song et al. [8] (2011)	7/M	4	Right hemifacial palsy	Yes	No	No	Typical (humeri, femurs, clavicle, ribs)	Chest	Brain	Bone	CS CT

Table 1 (continued)

Reference	No./ sex	Age of the onset	Extra-skeletal signs	Bone pain	Bone mass	Location	X-ray localization	CT scan	MRI	Type of histology sample	TT
Krishna et al. [23] (2014)	8/F	14	Focal thickening of the meninges	Yes	Yes	Forehead, right hand	Typical (long bones, calvarium skull, vertebrae)	Brain Bones	Brain	Bone	IFN-alpha
Alimohamadi et al. [25] (2015)	9/M	12	Right trigeminal neuralgia, diplopia	No	No	No	NR	Brain	Brain	Extra-axial mass	CT
Kim et al. [5] (2015)	10/ M	3	Exophthalmos	No	No	No	Typical (skull, tibiae, fibulae)	NR	Brain	Bone Brain	CT
Diamond et al. [22] (2016)	11/ M	5	Hearing loss, left hemifacial palsy	No	No	Four limbs	Long bones	Brain	Brain	Bone	Anakinra
White et al. [24] (2016)	12/ M	13	DI	No	No	No	No	Abdomen Pelvis	Brain	Brain	CS CT
Hao et al. [26] (2018)	13/ M	2	Exophthalmos	Yes	No	Four limbs	Typical (tibia, fibula, foot bones)	Brain	Brain	Brain	Dabrafenib
Romano et al. 2023	14/ M	17	Persistent diplopia	Yes	No	Four limbs	NR	NR	Bilateral neuromas (C5-D1)	Bone	Everolimus
Romano et al. 2023	15/ F	9	NR	No	No	No	NR	NR	Brain	Bone	IFN-alpha

CS, corticosteroids; CT, chemotherapy; CT scan, computerized tomography scan; DI, diabetes insipidus; F, female; GH, growth hormone; HSPM, hepatosplenomegaly; IFN-a, interferon-a; M, male; MDP, methylene diphosphonate; MRI, magnetic resonance imaging; N, normal; NR, not reported; TT, treatment.

therapies include MEK inhibitors (trametinib, cobimetinib), immunotherapy (interferon), imatinib, and mTOR inhibitors. Almost no disease progression has been observed under these regimens [2]. In selected cases, surgical debulking is required, for both the neurosurgical indications and the necessity of confirming the diagnosis [19–21], as happened in the 2 patient cases described previously. Indeed, our first patient with a 3-year history of migrant arthralgias presented at the last MRI scan a thickening of the cervical nerve roots and areas of nodular impregnation that marked the medullary cord, especially the C6-C7 level of the medullary cord, so a cervical laminectomy and subtotal exeresis of the lesions encountered were necessary to obtain decompression of the spinal cord and to obtain the lesion histology. In our second case, who had previously received the diagnosis of Langerhans cell histiocytosis, the MRI brain scan revealed the presence of an extra-axial lesion in the left temporopolar region, with dural implantation. Therefore, the patient received a left frontotemporal craniotomy with radical resection of the lesion. Histology was indicative of ECD. Differential diagnoses include infections, primary or metastatic CNS tumors, multiple sclerosis, granulomatous disease, and histiocytic tumors, from which differential diagnosis could be difficult. In addition to the nonspecific symptoms, the biopsy is not always diagnostic. Interestingly, in our first patient, the first bone marrow biopsy was proved negative, while the one realized after the cervical spine surgery was diagnostic of ECD. In our second patient, the surgery of sacral laminectomy and the lesion biopsy realized at the cone-cauda level was not diagnostic. In 2020, Goyal et al. [2] proposed consensus recommendations for the management of patients with ECD, remarking on the exceptional presentation in the pediatric population. ECD is exceptionally described in children and adolescents [4–14, 22–26], with 15 pediatric cases with involvement of the CNS currently described in the literature (Table 1) and no shared guidelines for the management of these patients. In these patients, some common findings were a deficiency of the hypothalamic/pituitary axis [9, 13, 24], involvement of the cranial nerves [8, 23, 25], and thickening of the meninges [5, 23], as well as radiological findings of meningioma-like lesions, as the second case described in this article. In addition, no disease activity score has yet reached a consensus. The typical appearance on X-ray is bilateral and symmetrical osteosclerosis affecting the meta-diaphyseal region of the long bones, especially at the knee (distal femur/proximal tibia). Its features include frequent involvement of the CNS, like in both of our two cases and frequent findings of mixed histiocytosis. That was the case of our second patient, whose initial diagnosis was Langerhans cell histiocytosis. The treatments adopted in the pediatric population are heterogeneous [6] and include, with good efficacy, IFN-a, vemurafenib, and chemotherapy (with schemes derived from those for LCH). In this case report, the first patient received everolimus (7 mg once a day), considering the systemic involvement, with significant improvement of his clinical condition, while the second one, considering the slow disease progression, received treatment with pegylated alpha interferon (180 μg, half vial once a week). During everolimus administration, pain significantly improved with less painkiller administration. Surprisingly, the pineal lesion showed an initial mass shrinkage in the last MRI, which probably confirmed the first histology wrong, probably due to its mistargeting during surgery.

Conclusion

The two cases described offer a picture of ECD manifestation in children and young adults, whose presentation is characterized by the involvement of the CNS and the association with other histiocytosis. Both cases received the histological diagnosis after a neurosurgical procedure. The first case received the diagnosis after a cervical spine biopsy and the second case after the excision of an extra-axial temporal lobe lesion. The pediatric population is exceptionally affected by ECD disease, so its documentation is often anecdotal. In addition, a uniform consensus for the diagnostic and therapeutic management of these patients has not yet been reached.

Statement of Ethics

The manuscript was reviewed and approved by the Pediatric Ethics Committee (Tuscany region), in the session of April 26, 2023. Written informed consent was obtained from legal guardians for publication of the details of their medical case and any accompanying images. No vulnerable patients have been included in this case series.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Carmine Romano: conceptualization, investigation, and writing of the original draft. Francesco Pegoraro, Matteo Lenge, and Chiara Spezzani: editing. Augusto Vaglio, Elena Sieni, Ilaria Fotzi, Andrea Di Rita, Simone Peraio, Alice Noris, Carla Gaggiano, and Salvatore Grosso: supervision. Flavio Giordano: conceptualization, supervision, and critical revision of the manuscript.

Data Availability Statement

No datasets were generated or analyzed for the current case report. Further inquiries can be directed to the corresponding author.

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