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Central nervous system-predominant Erdheim–Chester disease mimicking meningioma responding to BRAF inhibitor therapy: the importance of molecular diagnosis and targeted therapy in rare neoplastic disorders

Amrita Chakrabarti · Anirban Deep Banerjee · Ishani Mohapatra · Ritesh Sachdev · Bosky Jain · Nitin Sood

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Summary Erdheim–Chester disease (ECD) is a rare multi-system, non-Langerhans cell histiocytic disorder (NLCHD) with only a few hundred cases reported in the literature. Its diverse clinical manifestations require a high level of diagnostic suspicion. BRAFV600E mutation analysis is of critical significance, as it has implications for targeted therapy with BRAF inhibitors such as vemurafenib and dabrafenib. We report a case of symptomatic, central nervous system (CNS)-predominant ECD initially presenting with CNS mass lesions mimicking meningiomas on imaging and prominent periorbital xanthogranulomas. CNS presentation of ECD, although not infrequent, bears particular significance here from a therapeutic point of view, since only partial debulking was possible owing to anatomical complexities. Radiological evaluation following surgery showed no significant change in the size of the lesions. Targeted therapy was commenced following histopathology, immunohistochemistry (IHC), and molecular testing, resulting in marked improvement of clinical symptoms and tumor regression. Thus, diagnostic accuracy was imperative for symptomatic relief in this rare but aggressive neoplasm with a complex clinical presentation and misleading initial radiological impressions, bearing an otherwise grim prognosis.

Keywords Erdheim–Chester disease · BRAFV600E mutation · Vemurafenib · Non-Langerhans cell histiocytic disorder · CNS space-occupying lesions

A. Chakrabarti, MBBS, DNB · N. Sood, MBBS, MD, FRCPath
Department of Clinical Hematology & Bone Marrow Transplant, Medanta—The Medicity, Gurugram, India
dr.amritachakrabarti@gmail.com

A. D. Banerjee, MBBS, MCH (✉)
Institute of Neurosciences, Medanta—The Medicity, Gurugram, India
anirbandeepbanerjee@yahoo.com

I. Mohapatra, MBBS, MD · R. Sachdev, MBBS, MD
Department of Pathology, Medanta—The Medicity, Gurugram, India

B. Jain, MBBS, MD
Department of Radiodiagnosis, Medanta—The Medicity, Gurugram, India

Introduction

Erdheim–Chester disease (ECD) is a rare hematopoietic disease. It is an non-Langerhans cell histiocytic disorder (NLCHD) and is characterized by clonal histiocytic proliferation of multiple organs, mostly of the long bones. It is imperative to distinguish this disorder from Langerhans cell histiocytosis (LCH) for therapeutic relevance. The BRAFV600E mutation has been demonstrated in more than 50% of this disorder [1]. It has been considered to be a variably aggressive disease with unsatisfactory treatment outcomes. Only several hundred cases have been documented in literature, the majority over the past 10 years, mainly due to increased recognition and awareness of this disease [2]. The clinical manifestations are diverse, owing to lipid-laden histiocytic infiltration into various organs, resulting in presentations varying from focal disease to life-threatening organ failure [3]. The complex manifestations of this disease along with its rarity make it more prone to incorrect diagnosis, resulting in an overall poor prognosis. Literature review suggests there are no randomized controlled trials owing to lack of sufficient reported cases. A study conducted by Arnaud et al. [4] reports the 1-year and 5-year survival rates to be only 96% and 68%, respectively. Nevertheless, its diagnosis remains a clinical challenge and requires a high level of diagnostic suspicion. Pathologically, it needs to be differentiated from

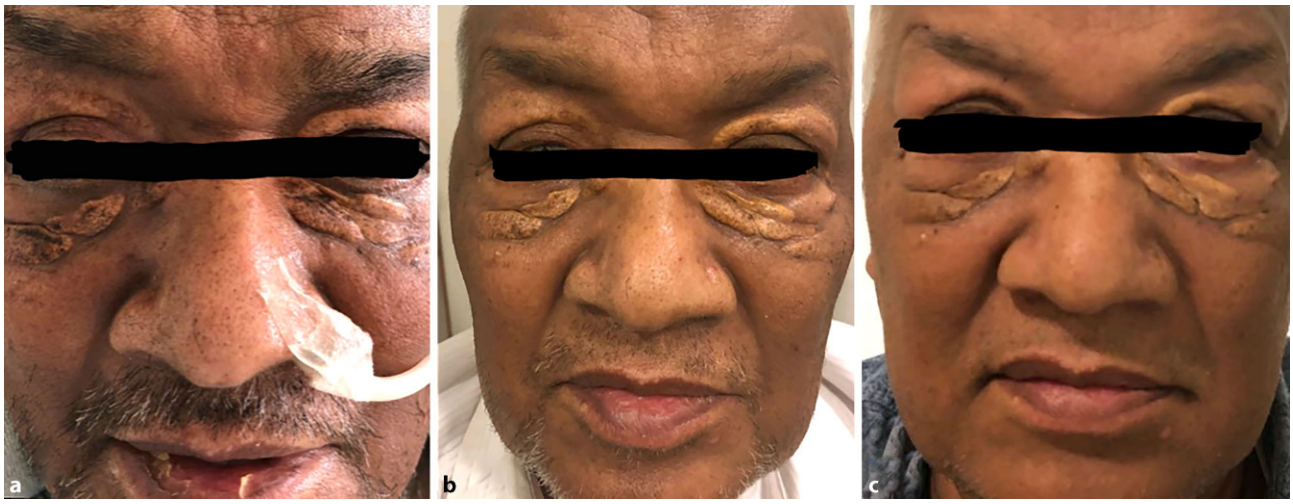


Fig. 1 **a** Pre-therapeutic prominent peri-orbital xanthelasma-like skin lesions. **b** Reduction of skin lesions following commencement of targeted therapy with vemurafenib. **c** Further significant improvement of peri-orbital xanthelasma following 3 months of targeted therapy with vemurafenib

LCH based on morphological, immunohistochemical, and molecular criteria. ECD has primarily been reported in adults between the 5th and 7th decade, with mean age being 55 years and a slight male predominance [5, 6].

Clinically, the symptoms are varied and non-specific, with involvement of multiple systems including the bones; central nervous system (CNS); heart; coronary and great vessels; lungs; retroperitoneum; kidneys; and, rarely, the skin, testes, breasts, skeletal muscles, thyroid, and gastrointestinal tract [3]. CNS manifestations are wide ranging, from asymptomatic to severe disability and death. Drier et al. [6] conducted a retrospective study of 33 patients with ECD and reported 45% to have CNS symptoms and/or orbital manifestations at presentation, including diabetes insipidus, exophthalmos, cerebellar ataxia, panhypopituitarism, and papilledema.

Therapy consists of limited alternatives with no universally formulated guidelines, and is considered to have a poor response due to the aggressive nature of the disease [1]. However, presence of the BRAFV600E mutation has potential therapeutic implications for targeted drugs such as vemurafenib and dabrafenib, along with other treatment options including interferon alpha/ pegylated interferon alpha (IFN-α/PEG-IFN-α), anticytokine-directed therapy (anakinra, infliximab, tocilizumab), corticosteroids, cytotoxic chemotherapies, radiotherapy, and surgery.

Here we report the case of 65-year-old male presenting with neurological symptoms, peri-orbital xanthogranuloma-like lesions, and intracranial space occupying lesions (SOLs) initially diagnosed as meningiomas on imaging. Histopathological, immunohistochemistry (IHC), and molecular testing later confirmed ECD. Targeted therapy with vemurafenib resulted in a favorable response, with alleviation of neurological symptoms and remarkable improvement of skin lesions. Following 3 months therapy with vemurafenib, repeat imaging was also favorable, showing shrinkage of lesions. The patient continues to be on vemurafenib and undergoes regular follow-ups for clinical, laboratory, and radiological assessment.

Case report

A 65-year-old diabetic and hypertensive gentleman with known history of empty sella syndrome who had been operated on for TP shunt presented to the emergency department with occipital headaches, gait imbalance, restricted neck movements, blurring of vision, and urinary incontinence of about 1 month's duration. Additionally, he had prominent periorbital xanthelasma-like lesions (Fig. 1a). Initial pre-op magnetic resonance imaging (MRI) revealed multifocal well-defined extra-axial infratentorial mass lesions along with a large foramen magnum lesion measuring 5.18 × 3.72 cm, consistent with meningiomas (Fig. 2a). Whole-body positron-emission tomography/computed tomography (PET CT) scan showed hypermetabolic extra-axial dural-based masses in the infratentorial compartment of the brain, diffuse osteosclerosis involving the appendicular skeleton and skull base, and possible early renal and vascular involvement (Fig. 3).

Only a partial excision of the lesion was possible owing to anatomical complexities, as the tumor had involved the right vertebral artery. Frozen section evaluation of the tissue was suggestive of NLCHD, which was later confirmed by formalin-fixed and paraffin-embedded sections, showing clusters of foamy histiocytes (Fig. 4). Extensive IHC studies were carried out, which were consistent with NLCHD (Fig. 5). Workup of various IHC markers, as demonstrated in the table, suggested a diagnosis of ECD, ruling out LCH and meningioma (Table 1).

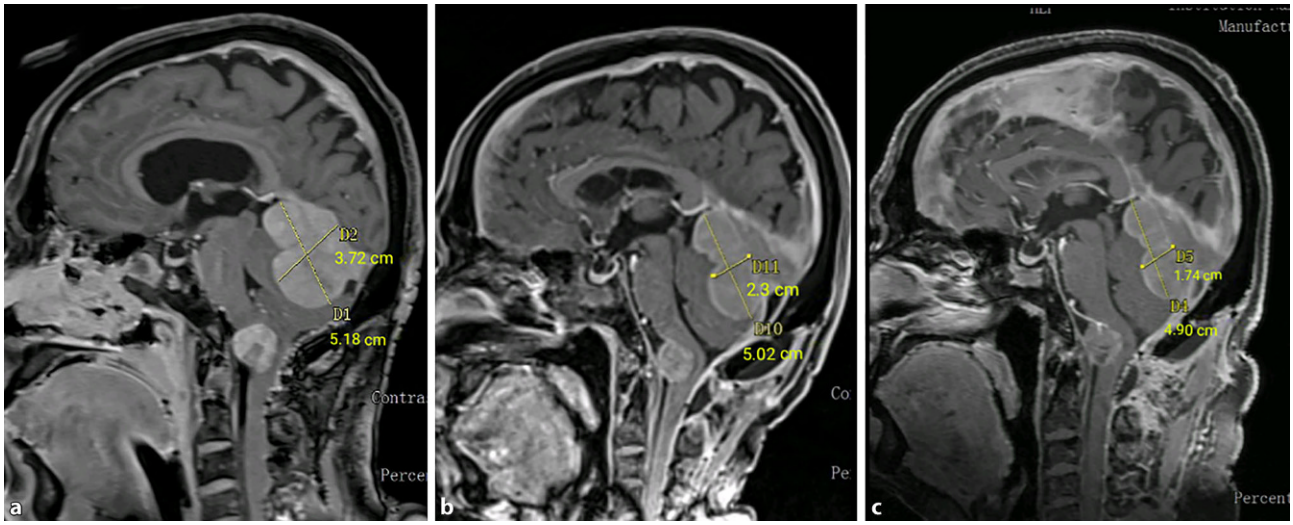
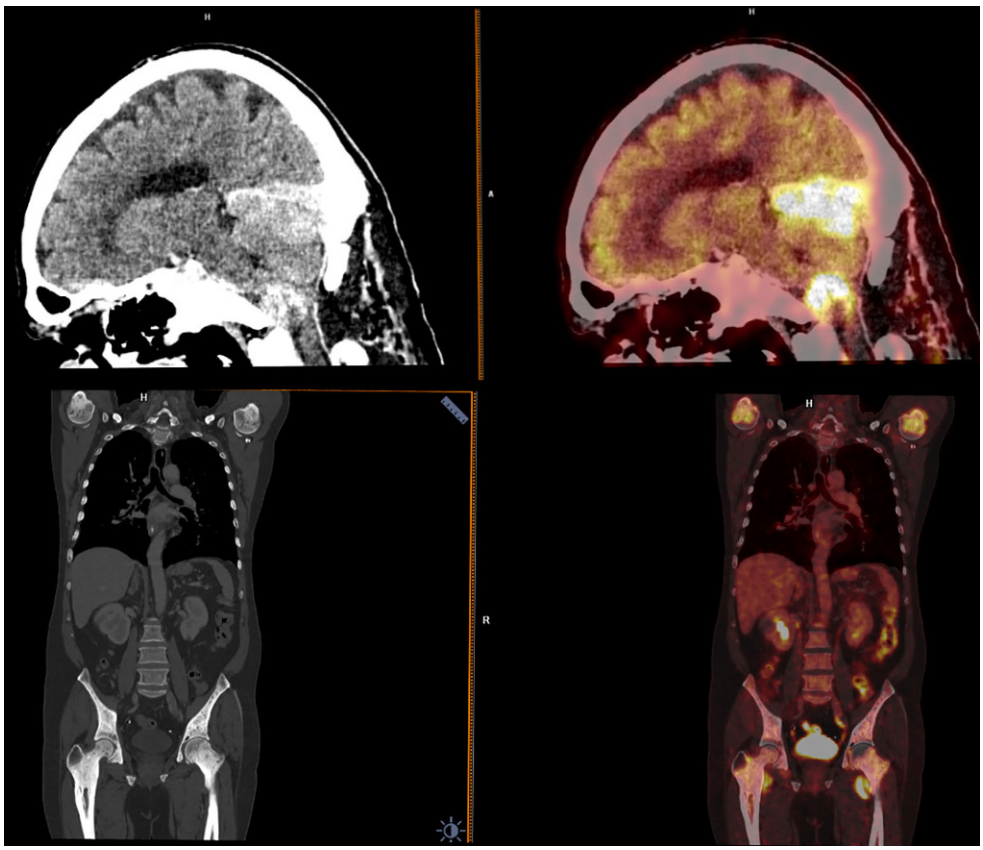


Fig. 2 **a** Initial pre-operative MRI sagittal section showing well-defined, well-enhancing extra-axial mass lesions in the infratentorial compartment. Another similar extra-axial lesion is seen at the anterior foramen magnum causing severe narrowing of the foramen magnum. **b** Post-operative MRI with sagittal section showing marginal interval change in the large extra-axial mass lesions in the infratentorial compartment and at the anterior foramen magnum. **c** MRI sagittal section on vemurafenib showing interval decrease in the sizes of the extra-axial mass lesions in the infratentorial compartment along the inferior surface of tentorium cerebelli. Intervals are denoted in *yellow*

Fig. 3 PET CT showing **a** hypermetabolic extra-axial dural-based masses in the infratentorial compartment of brain, **b** diffuse osteosclerosis involving the appendicular skeleton and skull base, and possible early renal and vascular involvement



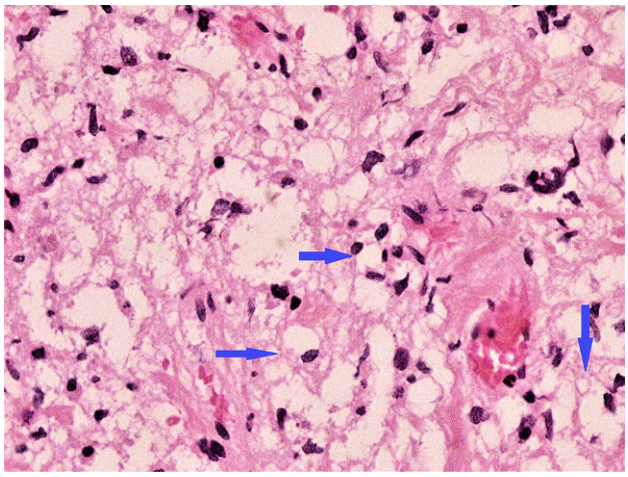


Fig. 4 *Arrow marks* showing clusters of histiocytes with clear cytoplasm. Hematoxylin & eosin stain × 400

S100 and CD1a were negative, which is characteristic of LCH. CK was also negative, which ruled out epithelial tumors such as meningioma. CD68 was positive, which confirmed a histiocytic proliferative disorder. Bone marrow aspiration and trephine biopsy were done subsequently for staging purposes. Biopsy revealed fibrosis with proliferation of lipid-laden histiocytes. IHC markers over bone marrow biopsy sections were consistent with that of the tissue, showing CD 68 positivity, S100 and CD1a negativity.

Mutation analysis was then carried out using the next generation sequencing (NGS) platform Ion Torrent Personal Genome Machine (Thermo-Fisher Scientific, USA). A 50-gene Ion AmpliSeq for Illumina Cancer Hotspot Panel was run, which demonstrated BRAF mutation. Other mutations detected were HRAS, KIT, PDGFRA, PIK3CA, and SMARCB1. However, those were silent mutations and not clinically significant.

Post-operative MRI showed only marginal interval change in the anterior foramen magnum mass, which now measured 5.02 × 2.3 cm (Fig. 2b). The patient continued to exhibit neurological symptoms of dizziness, gait imbalance, and reduced visual acuity. Targeted therapy with the BRAF inhibitor vemurafenib was then started. The patient responded favorably, as his skin lesions considerably reduced (Fig. 1b) along with marked alleviation of neurological symptoms. Following 3-month therapy with BRAF inhibitor targeted therapy, repeat MRI showed marginal interval decrease in the infratentorial extra-axial masses and that of the foramen magnum lesion, which now measured 4.90 × 1.74 cm (Fig. 2c). Clinically, his symptoms and signs improved further, including those of the periorbital lesions (Fig. 1c). We plan regular clinical, laboratory, and radiological follow-ups for the patient, while he continues to be on vemurafenib as prolonged therapy is generally indicated. Furthermore, significant radiological regression of lesions requires long-term use of targeted therapy.

Discussion

Histiocytic disorders are classified into LCH or "X type" histiocytoses and NLCH or "non-X type" histiocytoses. LCH includes diseases such as Hand–Schuller–Christian disease, Letterer–Siwe disease, and eosinophilic granuloma, while NLCHD comprises ECD and Juvenile xanthogranuloma (JXA). The etiology of ECD is unclear and it was earlier considered to be a non-neoplastic entity; however, the establishment of the BRAFV600E mutation has uncovered its oncogenic potential. This mutation had been observed between 38% and 68% of cases with ECD, as per literature review, with one study reporting it in 100% cases [1]. Moreover, the clonal nature of ECD is supported by its proinflammatory pattern. It has been established that the histiocytes express increased levels of cytokines and chemokines such as INF α and interleukin (IL)-12, and reduced IL-4 and IL-7 levels [7, 8]. Such proinflammatory states predispose to hyperactivation of mitogen-activated protein kinase (MAPK) signaling, hence elevating the neoplastic potential of this entity.

Owing to the diversity in presentation, treatment and prognosis of ECD vary as per the site of involvement and clinical manifestations. Diamond et al. [1] classify ECD according to clinical severity and organ system dominance. According to the study, ECD can be broadly classified into asymptomatic or minimally symptomatic, and symptomatic forms. Symptomatic ECD is further subclassified into CNS, cardiac, retroperitoneal, orbital-craniofacial, neuroendocrine, pulmonary-dominant forms, and multisystem-involvement disease. Our case could thus be referred to as symptomatic, CNS-dominant ECD.

Two different studies conducted by Arnaud et al. and Drier et al. report CNS involvement of ECD in 51% and 45% of cases, respectively [4, 6]. CNS manifestations commonly include DI, exophthalmos, cerebellar ataxia, panhypopituitarism, and papilledema [6]. It may also present as mass lesions of the hypothalamic–pituitary axis, dentate area of the cerebellum retro-orbital masses, and meningeal lesions of the dura. However, isolated involvement of the CNS has rarely been reported, with most cases affecting at least two other anatomical sites. The differential diagnoses of ECD with CNS involvement include a wide variety of conditions such as glial tumors; meningioma; demyelinating diseases; LCH or other inflammatory/granulomatous lesions of the supratentorium; and retro-orbital Wegener's granulomatosis. Lymphoma, sarcoidosis, and Sjogren's syndrome are other likely differential conditions [3, 9, 10].

Skin involvement is extremely rare in ECD and usually presents as xanthoma-like papules and periorbital xanthelasma-like skin lesions [5, 12]. A study conducted by Veyssier-Belot [11] reported skin involvement in 11 out of 59 patients presenting with ECD.

Histopathological findings along with relevant clinical and radiological features aid in the diagnosis of

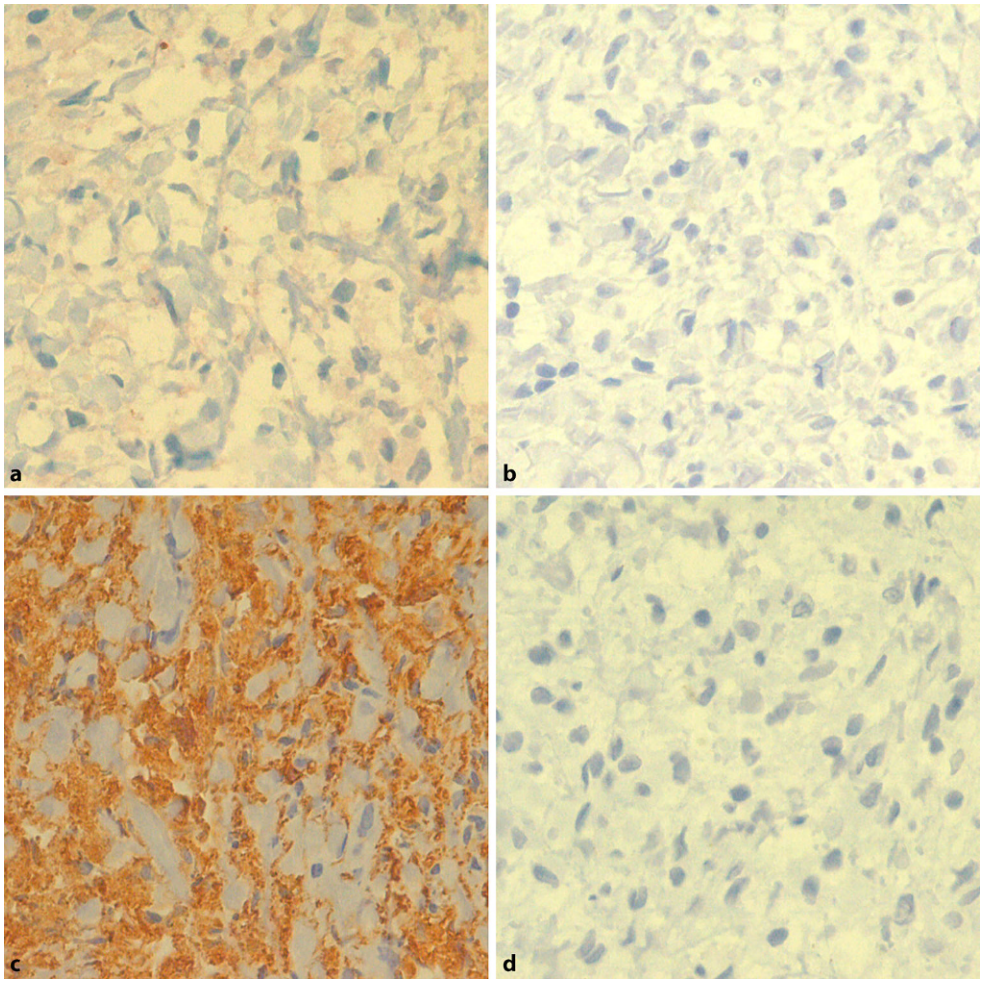


Fig. 5 **a** S100 (IHC stain × 400) negative to faint in sheets of histiocytes. **b** CK (IHC stain × 400) negative to faint in sheets of histiocytes. **c** CD 68 (IHC stain × 400) positive in sheets of histiocytes. **d** CD1a (IHC stain × 400) negative in sheets of histiocytes

ECD. It typically shows infiltration of foamy or lipid-laden histiocytes with admixed or surrounding fibrosis, with or without Touton giant cells. IHC staining of ECD histiocytes is positive for CD68, CD163, and factor XIIIa, and negative for CD1a and Langerin (CD207). S100 positivity has been observed rarely. IHC is essential for differentiating ECD from LCH as Langerhans cells are positive for CD1a, S100, and Langerin. JXG is considered to be a variant of ECD, as the histiocytes in both cases are morphologically and immunohistochemically identical [1]. MRI is the modality of choice for lesions involving the CNS [3, 6].

Generally, treatment is indicated in all cases of ECD except for the asymptomatic ones, which may be monitored only [1]. Literature review shows that INF α has been considered the first-line management strategy as it mostly provides sustainable stabilization [3, 4, 13]. Dosing varies from 3 to 9 million units three times per week. PEG-IFN-α is administered at 135 to 200 μg per week. Prolonged administration is required with these agents and the adverse effects include asthenia, myalgia, pruritus, thrombocytopenia, and depression [3]. Arnaud et al. [4] in their study demonstrated 46 out of 53 patients treated with IFN-α or PEG-IFNα interferon had significantly improved overall survival compared with other therapies. Another study encompassing 24 cases established the efficacy of high-dose IFN-α or PEG-IFNα in severe ECD. Interestingly, the treatment response was noted to be most prominent in cutaneous disease, followed by CNS, pituitary, lung, and heart disease [3]. However, it has been reported that INF-based treatment may result in adverse outcomes in CNS diseases compared to other organ involvements [1]. Surgical debulking may provide temporary relief, predisposes, however, to rapid re-growth of lesions [14]. Encouraging results have been obtained with certain targeted therapeutic agents such as anakinra, which is an IL1 receptor inhibitor, and vemurafenib, a BRAF inhibitor. Other potential drugs include tocilizumab (IL-6 R) and infliximab (anti TNFα).

Conclusion

Being a rare, multi-system disease, the diagnosis and treatment of ECD remain a challenge and require a multi-disciplinary approach along with a high level of pathological suspicion. There is lack of proper and adequate data regarding treatment guidelines. Hence, increasing the quality and duration of life are the

Table 1 IHC showing differentiation between ECD, LCH, and epithelial tumors (meningioma)

IHC features	ECD	LCH	Epithelial tumors (meningioma)
CD1a	–	+	–
S100	–	+	–
CK	–	–	+
CD68	+	+	–

IHC Immunohistochemistry, *ECD* Erdheim-Chester disease, *LCH* Langerhans cell histiocytosis, *CD* Cluster of differentiation, *CK* Cytokeratin

main treatment goals. However, recent studies have been promising in terms of developing molecular and immunologically targeted therapies. Histopathological findings remain the key to diagnosis, as clinical presentation may be wide and varied, while radiology is often misleading initially. BRAF mutation analysis is essential due to targeted therapy implications.

Hence, histopathological, immunohistochemical, and molecular diagnosis have imperative importance in the treatment and prognosis of certain rare disorders such as ECD that may have a wide range of differential diagnoses. Moreover, diagnostic relevance increases manifold where there is scope for targeted therapy, when conventional management and/or surgical intervention may not be adequate for satisfactory therapeutic outcomes.

Conflict of interest A. Chakrabarti, A.D. Banerjee, I. Mohapatra, R. Sachdev, B. Jain, and N. Sood declare that they have no competing interests.

Ethical standards Informed consent was obtained from the patient for which identifying information is included in this article.

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