Histiocytic Disorder Mimicking a Brain Tumor: A Report of 2 Rare Cases

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Case series
Patients: Male, 65-year-old • Female, 61-year-old
Final Diagnosis: Langerhans cell histiocytosis • Rosai-Dorfman disease
Symptoms: The patient with LHD presented with increasing memory loss, confusion, and depression • the patient with RDD presented with dizziness and confusion for three weeks and headaches for one day
Medication: —
Clinical Procedure: —
Specialty: Pathology

Objective: Rare disease
Background: Histiocytic disorders, a group of disorders with heterogeneous pathogenesis, morphology, and clinical presentation, include Rosai-Dorfman disease, Langerhans cell histiocytosis, and Erdheim-Chester disease. They can mimic primary or metastatic tumors, both clinically and radiologically, when involving the brain. Therefore, it is crucial to present and discuss cases of histiocytic disorder involving the central nervous system (CNS) to provide new information on disease presentation and diagnosis more. In this paper, we present 2 cases of histiocytic lesions involving the brain and mimicking primary brain tumors.

Case Report: Case 1: A 65-year-old man presented with increasing memory loss, confusion, and depression. CT scans showed an isolated 2.9×2.0×0.6 cm intracranial hypothalamic lesion. Case 2: A 61-year-old woman presented with dizziness and confusion for 3 weeks and headaches for 1 day. MRI showed a single 5.0×4.0×3.3 cm extra-axial, dural-based, avidly enhancing, well-defined lesion along the left parietal convexity causing mass effect upon the underlying brain parenchyma, left atrial effacement, and minimal vasogenic edema.

Conclusions: Histiocytic disorders are relatively rare in the CNS compared with other locations and mimic more common entities in the brain, such as glioma or metastatic tumors. Despite its rarity, one should remain aware of the condition and consider it in the differential diagnosis. This article provides a brief review and adds pivotal data to the literature.

Keywords: Brain • Histiocytic Disorders, Malignant • Histiocytosis, Langerhans-Cell • Histiocytosis, Sinus

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/935885
**Background**

Langerhans cell histiocytosis (LCH) is a clonal neoplastic proliferation of Langerhans cells typically presenting in childhood with a male predilection. LCH can be localized to a single site, can occur in multiple sites of a single system or can be more disseminated and multisystem. The WHO classification of LCH includes NOS, monostotic, polyostotic, and disseminated. The predominant sites of involvement in the solitary form are bone and adjacent soft tissue. Patients with the unifocal disease are usually older children or adults who most commonly present with a lytic bone lesion; solitary lesions at other sites present as mass lesions or enlarged lymph nodes. Patients with unisystem multifocal disease are usually young children presenting with multiple or sequential destructive bone lesions, often associated with adjacent soft-tissue masses. Patients with multisystem involvement are infants who present with fever, cytopenia, skin and bone lesions, and hepatosplenomegaly. The clinical course of LCH is related to the staging of the disease at presentation, with 99% survival for unifocal diseases and 66% mortality for young children with multisystem involvement who do not respond promptly to therapy. CNS involvement is rare, and isolated intracranial disease in adults is rarely reported [1-3].

Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a rare, idiopathic, non-neoplastic disorder that usually presents with massive painless lymphadenopathy, fever, leukocytosis, elevated erythrocyte sedimentation rate, and polyclonal hypergammaglobulinemia. Most cases of RDD occur during the first and second decades of life. The most common and prominent site of involvement is the cervical lymph nodes. Patients with localized nodal disease usually have a chronic, indolent course. Extranasal involvement of the liver, kidney, and lower respiratory tract, as well as signs of overt immune dysfunction are associated with poor prognosis. RDD rarely involves the CNS. The isolated intracranial disease is sporadic and can be mistaken for other pathologies in imaging studies [4].

Herein, we present a case of intracranial dural-based LCH initially considered a meningioma and a case of isolated RDD suspicious for glioblastoma.

**Case Report**

**Case 1**

A 65-year-old man presented with increasing memory loss, confusion, and depression. CT scans showed an isolated intracranial hypothalamic lesion. On magnetic resonance imaging (MRI), the lesion presented as a well-defined, inhomogeneous, enhancing mass involving the optic chiasm (Figure 1A, 1B) and suspicious for glioblastoma. The patient underwent surgical resection.

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**Figure 1.** On MRI, a 2.1×1.9×1.7 cm isolated, well-defined inhomogeneous hypothalamic-chiasmatic mass with associated vasogenic edema extending to the hypothalamic area, thalami, and upper midbrain was observed. (A) T1-weighted axial views with contrast. (B) T1-weighted sagittal views with contrast.
The specimen consisted of light brown soft-tissue fragments that measured 2.9×2.0×0.6 cm. On microscopic examination, abundant large histiocytes admixed with lymphocytes, plasma cells, and mature eosinophils were observed in a fibrous background. No necrosis or normal brain parenchyma was identified. The histiocytes revealed abundant pale eosinophilic cytoplasm and oval nuclei with irregular nuclear membranes, prominent nuclear grooves, fine chromatin, and indistinct nucleoli (Figure 2A-2D). The histiocytes were positive for CD1a, CD68, S100, and focally positive for Langerin (Figure 2E-2H). Morphologic and immunohistochemical features were diagnostic of LCH. The patient subsequently died due to complications of hypothyroidism, adrenal insufficiency, and post-surgical diabetes insipidus.
Case 2

A 61-year-old woman presented with dizziness and confusion for 3 weeks and headaches for 1 day. MRI showed a single 5.0×4.0×3.3 cm extra-axial, dural-based, avidly enhancing, well-defined lesion along the left parietal convexity causing a mass effect on the underlying brain parenchyma, left atrial effacement, and minimal vasogenic edema (Figure 3A, 3B). Meningioma was initially considered. After a complete work-up, the mass was resected.

The surgical specimen consisted of pink-tan tissue fragments measuring 0.9×0.7×0.3 cm and 5.3×3.8×0.3 cm, respectively. As shown in Figure 4A-4D, the H&E-stained slides demonstrated brain parenchyma diffusely infiltrated by histiocytes (hollow arrows; C, D) surrounded by extensive lymphoplasmacytic cells and abundant eosinophils (black arrows; C, D). The enlarged histiocytes had abundant pale eosinophilic cytoplasm, elongated bean-shaped nuclei, distinct nucleoli, and nuclear grooves. (A: 20×; B: 100×; C: 200×; D: 400×). Histiocytes showed CD1a (E), CD68 (F), and S100 (G) positivity, as well as Langerin focally positivity (H).

**Figure 2.** Pathologic features of LCH. (A-D) H&E stains at different magnifications demonstrated brain parenchyma diffusely infiltrated by histiocytes (hollow arrows; C, D) surrounded by extensive lymphoplasmacytic cells and abundant eosinophils (black arrows; C, D). The enlarged histiocytes had abundant pale eosinophilic cytoplasm, elongated bean-shaped nuclei, distinct nucleoli, and nuclear grooves. (A: 20×; B: 100×; C: 200×; D: 400×). Histiocytes showed CD1a (E), CD68 (F), and S100 (G) positivity, as well as Langerin focally positivity (H).

**Figure 3.** Isolated extra-axial dural-based parietal lobe mass measuring 5.0×4.0×3.3 cm was present MRI. (A) T1-weighted axial views with contrast. (B) T1-weighted sagittal views with contrast.
Immunohistochemically, the histiocytes were reactive to CD68 and S100 but negative for CD1a (Figure 4E-4G). In-situ hybridization (ISH) stains demonstrated polyclonal CD138-positive plasma cells (Figure 4H-4J). The morphological and immunohistochemical profiles and ISH studies were diagnostic of RDD.

**Discussion**

Based on the most recent classification of histiocytic lesions, which consist of 5 groups of diseases (L, C, R, M, and H) [5], LCH belongs to the L group, which also includes intermediate cell histiocytosis (ICH), Erdheim-Chester disease (ECD), and...
mixed LCH/ECD, while RDD is classified as “C” or “R” group depending on the location, as shown in Table 1.

About 4-25% of LCH cases involve the CNS clinically. Cases most frequently present with pituitary dysfunction, including diabetes insipidus and mass effect secondary to intra-axial or extra-axial lesions. Radiologists describe the CNS findings as tumorous/granulomatous lesions or non-tumorous/non-granulomatous lesions (neurodegenerative) or atrophic [6]. However, considerable overlap between these subgroups and findings of all 3 subgroups can occur in a single patient.

Intracranially, the characteristic radiologic lesion involves the hypothalamic-pituitary axis with an enhancing suprasellar mass and thickening of the infundibular stalk. Loss of the standard hyperintense signal on T1-weighted images from the posteri- or pituitary may also be detected. Calvarial bone lesions show preferential involvement of the outer table compared to the inner table, thus producing a classic “bone in bone” appearance. An associated scalp or soft-tissue component is often seen [7]. In our case, the isolated intracranial LCH occurred as is most commonly observed in the hypothalamic area, although the patient presented with confusion without pituitary symptoms. However, the patient reported having mild memory loss for a few months with sudden exacerbation over a few days before presenting to the Emergency Department. In addition, the patient reportedly had a recent fall requiring a cane to enable balance. Diabetes insipidus was not present before the craniotomy. Tan et al reported a similar case that occurred in the seller area in a 50-year-old woman. Their pa- tient presented with DM-like symptoms, polydipsia, and poly-uria, for over 3 months [8].
Table 1. 2016 Revised classification of histiocytosis and neoplasms of the macrophage-dendritic cell lineages.

| Group | Subgroup |
|-------|----------|
| **L group** | Langerhans cell histiocytosis (LCH) | Indeterminate cell histiocytosis (ICH) |
|       | Erdheim Chester diseases (ECD) | Mixed LCH/ECD |
|       | Cutaneous non-LCH | Xanthogranuloma (XG)Family |
|       | Juvenile xanthogranuloma (JXD) | Adult xanthogranuloma (AXD) |
|       | Solitary reticulohistiocytoma (SRH) | BCH |
|       | GEH | Progressive nodular histiocytosis (PNH) |
|       | Non-XG family | Cutaneous Rosia-Dorfman Disease (RDD) |
|       | Necrobiotic xanthogranuloma (NXG) | Other NOS |
|       | Cutaneous non-LCH with a major systemic component | XG family |
|       | Non-XG family | Progressive nodular histiocytosis (PNH) |
|       | Familial Rosai-Dorfman Disease | Sporadic RDD |
|       | Classical RDD | Extra-nodal RDD |
|       | RDD with neoplasia or immune disease | Unclassified |
| **R group** | Primary Malignant Histiocytoses | Secondary Malignant Histiocytoses |
| **M group** | Primary Histiocytes of the H group (HLH): Mendelian inherited conditions leading to HLH | Secondary HLH (non-Mendelian HLH) |
| **H group** | HLH of unknown/uncertain origin | |

It is adapted from: “Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages” by Emile JF, et al. Blood. 2016; 127(22): 2672-2681.

Microscopically, the LCH cells are oval with grooved, folded, indented, or lobed nuclei with fine chromatin, inconspicuous nucleoli, and thin nuclear membranes. The cytoplasm is moderately abundant and slightly eosinophilic. A variable number of eosinophils, histocytes, neutrophils, and small lymphocytes are present. Plasma cells are sparse. The classic morphologic features were present in our case. In the early stage, LCH cells predominate, along with eosinophils and neutrophils, while in the late stages of the disease, the LCH cells are decreased, with increased foamy macrophages and fibrosis. Tumor cells consistently express CD1a, langerin, and S100 protein. Crucial immunohistochemical stains differentiate LCH from other histiocytic lesions, including CD1a, Langerin, S100, CD68, HLA-DR, and vimentin. The ultrastructural hallmark of LCH is the cytoplasmic tennis-racket-shaped Birbeck granules.

LCH should be differentiated from Erdheim-Chester disease. The latter is considered another clonal systemic histiocytic proliferative disease involving any organ and tissue belonging to the “L” group, just like LCH. The clinical and radiological features can be very similar between the 2 diseases. However, skeletal involvement occurs in 95% of ECD cases, and there is typically bilateral and symmetric involvement of the long bones, which is much less common in LCH. CNS involvement occurs in 20-30% of patients with ECD and produces variable symptoms depending on tumor location. The most severe neurological complication is a neurodegenerative cerebellar disease, present in 15-20% of patients with ECD. CNS involvement is a significant prognostic factor, constituting an independent predictor of death. Morphologically, the lesional histocytes have single small nuclei and foamy or compact eosinophilic cytoplasm. Touton cells with a central ring of nuclei are frequently observed. Fibrosis is present in most cases and is sometimes abundant. Reactive small lymphocytes, plasma cells, and neutrophils are frequently present. The infiltration is easily misdiagnosed as a reactive process. The ECD histocytes can express the typical macrophage markers – CD14, CD68, and CD163 – but lack the Langerhans cell markers CD1a, S100, and langerin. Notably, up to 20% of patients with ECD also have Langerhans cell histiocytosis [5], and BRAF V600E mutation is reported in 50% of both LCD and ECD [10].
Table 2. Comparison of CNS involvement of three most common histiocytic lesions.

|                      | LCD                   | ECD                        | RDD                                    |
|----------------------|-----------------------|----------------------------|----------------------------------------|
| **Epidemiology**     | Mostly occur in childhood and male predominant | Mean patient age at diagnosis is 55-60 year, with male predilection. Pediatric cases are reported as well | Most cases occur in adolescent and young adult with African American predilection |
| **Most common location of CNS involvement** | Hypothalamic-pituitary axis | Hypothalamic-pituitary axis and meningeal involvement, cranial lesion | Dural based lesions |
| **Clinical features** | Diabetes insipidus followed cranial involvement. Skull and mandibular involvement are common | Diabetic insipidus and severe neurodegenerative cerebellar disease | Mimic meningioma |
| **Morphological features** | Neoplastic histocytes containing kidney shaped nuclei with grooves and reactive eosinophils in the background. Birbeck granules are typical ultrastructural features | Neoplastic foamy histocytes and Touton cells. Reactive inflammatory and fibrosis may present | Lesional histocytes with emperipolesis and reactive abundant mature plasma cells. Dutcher bodies may be prominent |
| **Immunophenotype**  | S100+, CD1a+, Langerin +; CD68+ | CD68+; S100-; CD1a-, Langerin- | CD68+; S100+, CD1a+, Langerin- |
| **Genetic profiles** | ~50% cases demonstrate BARF V600E mutation | ~50% cases demonstrate BARF V600E mutation | No evidence of clonality |

Therefore, immunohistochemical stains should be used to distinguish these entities instead of BRAF V600E mutation. Careful evaluation of our case did not reveal an ECD component. Another critical issue is that histopathology and phenotype are not distinct between ECD and extracutaneous or disseminated juvenile xanthogranuloma. When suspected ECD patients do not present with typical bilateral and symmetric involvement of the long bones, molecular testing should be performed.

Most cases of Rosai-Dorfman disease occur during the first and second decade of life and typically manifest as cervical lymph node enlargement, but other peripheral or central lymph node groups can be affected. In over 25% of the cases, RDD involves extranodal sites, including the CNS. Cerebral involvement usually manifests as dural-based lesions, often clinically and radiologically mistaken for meningiomas, just like this case. Intraparenchymal involvement is far less common, typically mimicking lymphoma or intraparenchymal tuberculobos granulomas. Furthermore, intraventricular lesions have been reported in some cases. Involvement of the intramedullary spinal cord, cavernous sinus, and retroocular region of the orbit is infrequent. No neurodegenerative pattern has been described in patients with RDD, unlike LCH and ECD [11-14]. Histologically, the lesions consist of numerous characteristic large histiocytes enmeshed in a variably cellular mixed inflammatory infiltrate composed of plasma cells often containing Russell bodies, lymphocytes, neutrophils, foamy macrophages, and rare eosinophils. The large histiocytes contain abundant eosinophilic cytoplasm and demonstrate emperipolesis with intracytoplasmic lymphocytes, plasma cells, or neutrophils. The nuclei of histiocytes range from round or oval to kidney bean-shaped with fine or vesicular chromatin and prominent nucleoli, which can be large. The histiocytes are variable in number and distribution. Microabscesses may be present. The large histiocytes express S100, CD68, and CD163 and are negative for CD1a, as shown in the present case. Molecular studies on involved tissue fail to demonstrate evidence of clonality, in keeping with their presumed reactive nature. The comparisons of the pathological features among the most common histiocytic disorders with CNS involvement are shown in Table 2.

**Conclusions**

LCD, ECD, and RDD are the most common histiocytic lesions with morphologic similarities. They are rarely involved in the CNS and present similar clinical and radiological features with primary CNS tumors. In this report, both cases of histiocytic lesions involving the brain were initially diagnosed as primary brain tumors clinically. Our experiences will help in accurate diagnoses of those entities involving the brain. As mimics of meningioma or glioma, histiocytic lesions should be included in the differential diagnoses due to the similarity of clinical symptoms and radiology features among those entities.
Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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