Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 32s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Clinicopathological Characterization of Central Nervous System and Spinal Histiocytosis: A Three-Case Series Including Langerhans and Non-Langerhans Cell Subtypes

Bilal Ibrahim[1], Abdallah Arabyat[2], Mohammad Y. Hiasat[3], Waleed F. Dabbas[1]

[1]Division of Neurosurgery, Department of Special Surgery, Faculty of Medicine, Al-Balqa Applied University, Al-Salt, Jordan

[2]AlHussain New Salt Hospital, Ministry of Health, Al-Salt, Jordan

[3]Department of Neurosurgery, Neuron Clinics, Amman, Jordan

***Corresponding Author**

Dr. Bilal Ibrahim

Division of Neurosurgery, Department of Special Surgery, Faculty of Medicine, Al-Balqa Applied University, Al-Salt, Jordan

Email ID: Bilal.Ibrahim@bau.edu.jo

Cite this paper as: Bilal Ibrahim, Abdallah Arabyat, Mohammad Y. Hiasat, Waleed F. Dabbas, (2025) Clinicopathological Characterization of Central Nervous System and Spinal Histiocytosis: A Three-Case Series Including Langerhans and Non-Langerhans Cell Subtypes. *Journal of Neonatal Surgery*, 14 (32s), 8109-8118.

ABSTRACT

Background:

Histiocytic disorders of the central nervous system (CNS) and spine are rare and diagnostically complex, requiring integration of clinical, radiological, histopathological, and molecular data. Recent classifications emphasize molecular alterations, including ALK gene fusions, which define ALK-positive histiocytosis as a distinct, therapeutically actionable entity. Accurate subclassification is essential for effective treatment.

Case Reports:

We report three cases representing different CNS histiocytic subtypes.

Case 1: A 27-year-old male presented with progressive lower limb weakness and radicular pain. MRI showed an intradural lesion initially suspected to be a schwannoma. Histopathology and immunohistochemistry confirmed ALK-positive histiocytosis, with KIF5B-ALK fusion detected by RT-PCR. Complete resection led to full neurological recovery with no recurrence at 4 years.

Case 2: A 36-year-old male presented with headaches and focal seizures. Imaging revealed a dural-based lesion mimicking meningioma. Histopathology demonstrated Rosai-Dorfman disease with emperipolesis and an S100-positive, CD1a-negative immunophenotype. The patient remains disease-free at 2 years post-resection.

Case 3: A 36-year-old male with vertebral Langerhans cell histiocytosis (LCH) presented with back pain and radiculopathy. Diagnosis was confirmed by CD1a and Langerin positivity; BRAF V600E mutation testing was negative.

Conclusions:

This series highlights the diagnostic challenges of CNS histiocytic disorders and underscores the value of comprehensive histopathological, immunohistochemical, and molecular profiling. Subclassification facilitates accurate diagnosis and guides individualized treatment, including the potential use of targeted therapies.

1. INTRODUCTION

Histiocytic disorders of the central nervous system (CNS) are rare, diagnostically complex entities arising from aberrant proliferation of dendritic cells or macrophages. These disorders are categorized according to revised criteria proposed by the Histiocyte Society, which emphasize both histogenesis and molecular alterations rather than morphology alone [1]. The classification includes Langerhans cell histiocytosis (LCH) and various non-Langerhans cell histiocytoses, including Rosai-Dorfman disease, Erdheim-Chester disease, and the recently recognized ALK-positive histiocytosis [1]. Accurate diagnosis requires integration of histopathological analysis, immunohistochemistry, and molecular diagnostics.

Langerhans cell histiocytosis represents the most well-characterized CNS histiocytic disorder, arising from clonal proliferation of dendritic cells with characteristic CD1a and Langerin expression [2,3]. Pathogenesis is closely linked to activating mutations in the MAPK pathway, particularly BRAF V600E and MAP2K1, which serve as both diagnostic markers and therapeutic targets [2,3]. CNS involvement, while uncommon, most frequently affects the hypothalamic-pituitary axis, but can also present as lytic bone lesions of the skull and spine with potential neurological complications [4,5]. The identification of BRAF mutations has therapeutic implications, as targeted therapy with BRAF inhibitors has shown efficacy in refractory cases [5].

Rosai-Dorfman disease is a benign histiocytic disorder characterized by accumulation of S100-positive, CD1a-negative histiocytes exhibiting emperipolesis—the pathognomonic finding of intact lymphocytes within histiocytic cytoplasm [6,7]. CNS involvement is rare but typically manifests as dural-based masses that can mimic meningiomas on neuroimaging, often leading to diagnostic delays [6,7]. The extranodal variant affecting the CNS requires careful immunohistochemical characterization to distinguish it from other histiocytic proliferations and more common CNS neoplasms [7].

ALK-positive histiocytosis represents a unique molecularly defined histiocytic disorder characterized by ALK gene rearrangements, most frequently KIF5B-ALK fusions [10,11]. This entity typically expresses strong ALK immunopositivity while lacking conventional histiocytic markers, creating diagnostic challenges that necessitate molecular confirmation [11,12]. Neurological involvement can affect brain parenchyma, meninges, and spinal structures, often mimicking nerve sheath tumors [12]. The recognition of this disorder as therapeutically actionable, with documented responses to ALK inhibitors, has significant clinical implications for patient management [12].

The differential diagnosis of CNS histiocytic disorders relies heavily on integrating morphological features with specific immunophenotypic profiles and molecular alterations. However, overlapping clinical presentations and radiological appearances can create diagnostic challenges, particularly when lesions involve unusual anatomical locations or present with atypical features. The rarity of these entities and their potential mimicry of more common CNS neoplasms necessitate increased clinical awareness and systematic diagnostic approaches. We present three cases of CNS histiocytic disorders ALK-positive histiocytosis, Rosai-Dorfman disease, and Langerhans cell histiocytosis to illustrate the diagnostic challenges, immunohistochemical differentiation, and molecular characterization strategies essential for accurate classification and optimal patient management.

2. MATERIALS AND METHODS

This case report presents a single patient with histologically and molecularly confirmed ALK-positive histiocytosis involving a spinal nerve root, identified through retrospective review of surgical pathology records. Written informed consent was obtained in accordance with institutional review board guidelines and Declaration of Helsinki ethical principles. Comprehensive clinical evaluation included detailed medical history, systematic neurological examination using standardized assessment criteria, and documentation of presenting symptoms with temporal progression analysis.

Advanced neuroimaging was performed using magnetic resonance imaging of the lumbar spine on a 1.5-Tesla scanner, incorporating T1-weighted, T2-weighted, and FLAIR sequences in sagittal and axial planes. Gadolinium-enhanced T1-weighted sequences were obtained following intravenous contrast administration at 0.1 mmol/kg body weight, with image analysis performed by board-certified neuroradiologists. Surgical intervention consisted of L2-L3 laminectomy with microscopic tumor resection under general anesthesia, employing intraoperative neurophysiological monitoring including somatosensory evoked potentials and electromyography to preserve neurological function and confirm nerve root localization.

The surgically resected specimen underwent standard histopathological processing, with tissue fixation in 10% neutral-buffered formalin, routine processing, and paraffin embedding. Serial 4-μm sections were prepared for morphological evaluation using hematoxylin and eosin staining, followed by comprehensive immunohistochemical analysis using automated systems. The antibody panel included anaplastic lymphoma kinase (ALK, clone D5F3), CD68 (clone PG-M1), S100 protein, and CD1a, performed with appropriate positive and negative controls and interpreted by board-certified pathologists with expertise in histiocytic disorders.

Molecular genetic analysis for ALK gene rearrangement was performed using reverse transcription polymerase chain reaction on formalin-fixed, paraffin-embedded tissue. RNA extraction, complementary DNA synthesis, and PCR amplification were conducted using standard protocols with primers specific for KIF5B-ALK fusion transcripts, followed by agarose gel electrophoresis and DNA sequencing for fusion confirmation. Comprehensive systemic evaluation to exclude multisystem involvement included physical examination, laboratory studies, and whole-body 18F-fluorodeoxyglucose positron emission tomography-computed tomography imaging.

Postoperative assessment followed standardized clinical protocols with immediate neurological evaluation within 24 hours of surgery, short-term follow-up at regular intervals, and long-term surveillance consisting of serial MRI imaging at 6-month intervals for two years, then annually thereafter. Clinical data were collected and analyzed according to CARE statement recommendations, with outcomes assessed over a minimum 4-year follow-up period to provide meaningful prognostic

information.

3. RESULTS

To highlight the clinicopathological variability observed in this cohort, we present three representative cases from each histiocytosis subtype:

Case 1: ALK-Positive Histiocytosis (L3 Sensory Nerve Root)

A 27-year-old previously healthy male presented with a 3-month history of progressive left lower limb weakness and radicular pain radiating from the lower back to the left leg. The patient reported difficulty with walking and progressive weakness in left foot dorsiflexion and toe extension. There was no history of recent trauma, fever, or systemic symptoms. Past medical history was unremarkable with no prior neurological complaints.

Neurological examination revealed significant motor deficits in the left lower extremity. Left knee flexion and plantar flexion strength was reduced to 4/5, while extensor hallucis longus strength was completely absent (0/5). Sensory examination demonstrated decreased sensation in the L3 dermatome distribution on the left side. Deep tendon reflexes were preserved bilaterally. The remainder of the neurological examination, including upper extremity function and cognitive assessment, was normal.

Magnetic resonance imaging of the lumbar spine revealed an intradural, extramedullary lesion at the L3 level. The mass measured approximately 1.8 cm in greatest dimension and demonstrated heterogeneous signal intensity on T2-weighted images (Figure 1A). Post-contrast T1-weighted imaging showed strong heterogeneous enhancement of the lesion (Figure 1B). The radiological appearance and intradural location were consistent with a nerve sheath tumor, most likely a schwannoma, prompting surgical intervention. Radiological imaging revealed an intradural lesion with radiographic features suggestive of a nerve sheath tumor, prompting surgical intervention. These findings are shown in Figure 1.

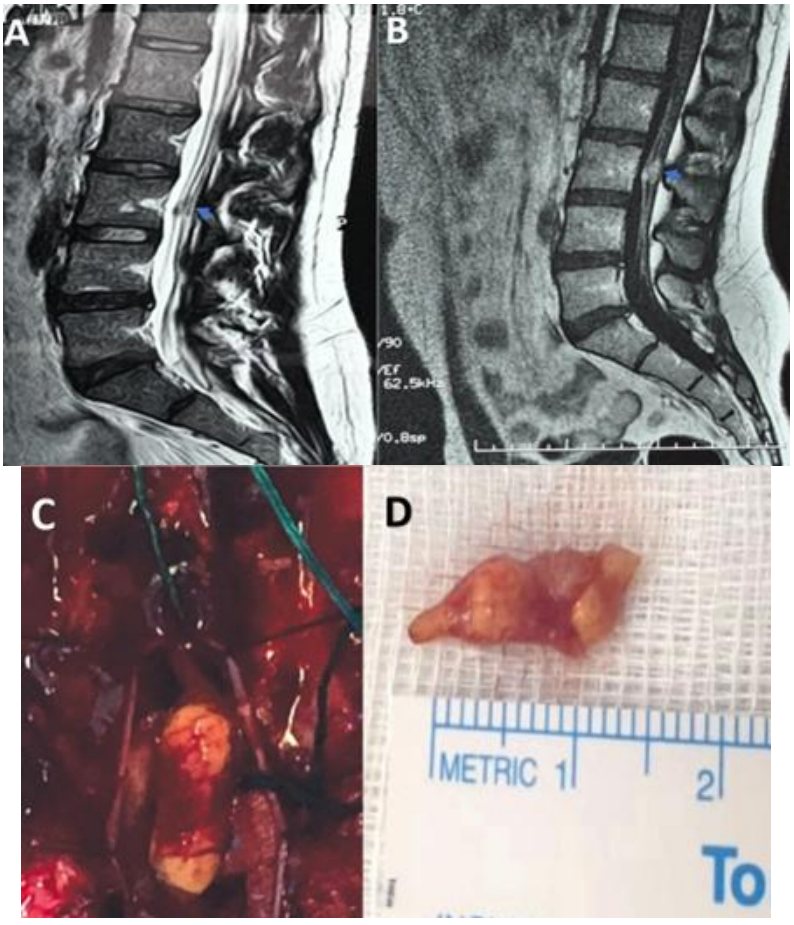

Figure 1. Imaging and intraoperative documentation of ALK-positive histiocytosis involving L3 sensory nerve root.

(A) Sagittal T2-weighted MRI shows an intradural lesion at L3 level. (B) Post-contrast T1-weighted MRI demonstrates strong heterogeneous enhancement of the mass. (C) Intraoperative image following L2–L3 laminectomy, revealing the tumor within the opened dura which originated from L3 sensory nerve as confirmed intraoperatively by neuromonitoring. (D) Gross specimen of the completely excised tumor measuring approximately 1.8 cm, later confirmed as ALK-positive histiocytosis.

The patient underwent L2-L3 laminectomy under general anesthesia with intraoperative neurophysiological monitoring. Upon opening the dura, a well-circumscribed, tan-colored mass was identified arising from the L3 sensory nerve root (Figure 1C). Intraoperative neuromonitoring confirmed the sensory nature of the affected nerve root, allowing for complete tumor resection including the involved nerve segment. The tumor was successfully removed en bloc, measuring 1.8 cm × 1.2 cm × 1.0 cm (Figure 1D). The procedure was completed without complications, and the patient tolerated the surgery well.

Microscopic examination revealed a proliferation of histiocytes with abundant eosinophilic to foamy cytoplasm and folded to smooth-round nuclei. Rare Touton-type giant cells were observed, along with mild mitotic activity. No areas of necrosis were identified. The morphological features were characteristic of a histiocytic proliferative disorder rather than a typical nerve sheath tumor. Immunohistochemical analysis demonstrated strong cytoplasmic positivity for anaplastic lymphoma kinase (ALK1) and CD68, confirming the histiocytic lineage. Critically, the tumor cells were negative for S100 protein and CD1a, excluding Langerhans cell histiocytosis and schwannoma. Additional testing for BRAF V600E was negative.

Molecular analysis using reverse transcription polymerase chain reaction (RT-PCR) revealed the presence of a KIF5B-ALK fusion transcript, providing definitive molecular confirmation of ALK-positive histiocytosis. Post-operatively, the patient experienced immediate improvement in radicular pain symptoms with progressive neurological recovery. At 6-month follow-up, left lower extremity strength had returned to normal (5/5 in all muscle groups). Serial MRI imaging at 6 months, 1 year, 2 years, and 4 years post-operatively showed no evidence of tumor recurrence. Comprehensive systemic evaluation including PET-CT imaging was negative for evidence of systemic histiocytic involvement. Histopathological features are shown in Figure 2, demonstrating abundant eosinophilic cytoplasm, nuclear irregularity, and a Touton-type multinucleated giant cell. Histological findings further confirmed the diagnosis of ALK-positive histiocytosis and are demonstrated in Figure 2.

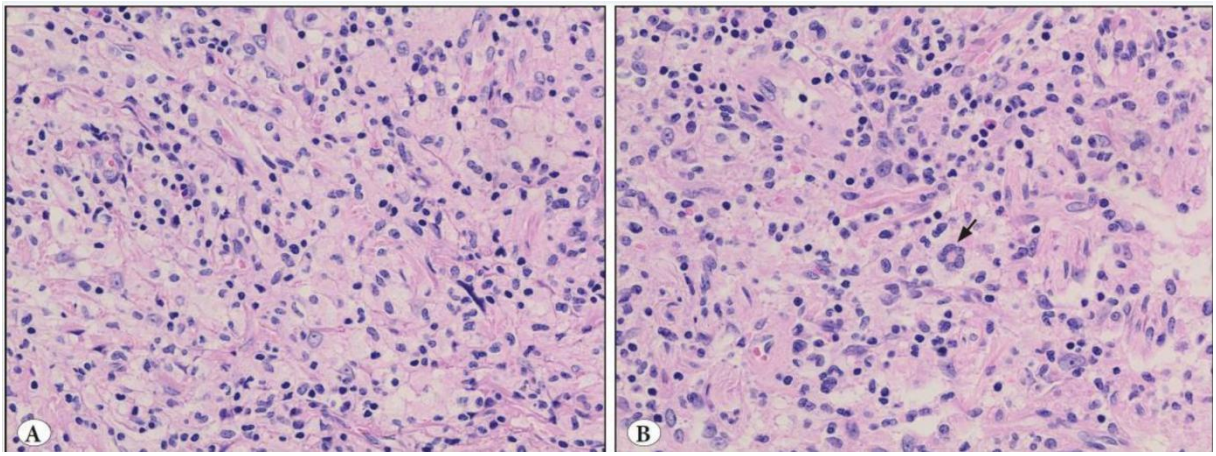

Figure 2. Histopathologic features of ALK-positive histiocytosis.

(A) Sheets of histiocytes with eosinophilic to clear cytoplasm, round to irregular nuclei, and occasional prominent nucleoli (H&E, ×400).

(B) A Touton-type multinucleated giant cell is identified (arrow) among the histiocytic population (H&E, ×400).

Images used with permission from Jaber et al., 2021. Licensed under CC BY 4.0.

(Jaber OI, Jarrah DA, Hiasat M, Al Hussaini M. ALK-positive histiocytosis: A case report and literature review. Turkish Journal of Pathology. 2021;37(2):172.)

Case 2: Rosai-Dorfman Disease (Left Parietal Dura)

A 36-year-old previously healthy male presented with a 2-month history of progressive headaches and focal seizures involving the right upper extremity, accompanied by episodes of dysphasia and dizziness. Physical examination revealed right shoulder abduction weakness (4/5 strength) with otherwise normal neurological function. There was no evidence of systemic symptoms, lymphadenopathy, or skin lesions.

Magnetic resonance imaging revealed a dural-based left parietal lesion measuring approximately 4.8 × 3.2 cm with surrounding vasogenic edema involving the left parietal lobe. The lesion demonstrated isointense signal on FLAIR sequences (Figure 3A) and homogeneous gadolinium enhancement on T1-weighted post-contrast imaging (Figure 3B). The radiological appearance was consistent with a convexity meningioma with potential pial invasion, prompting surgical intervention.

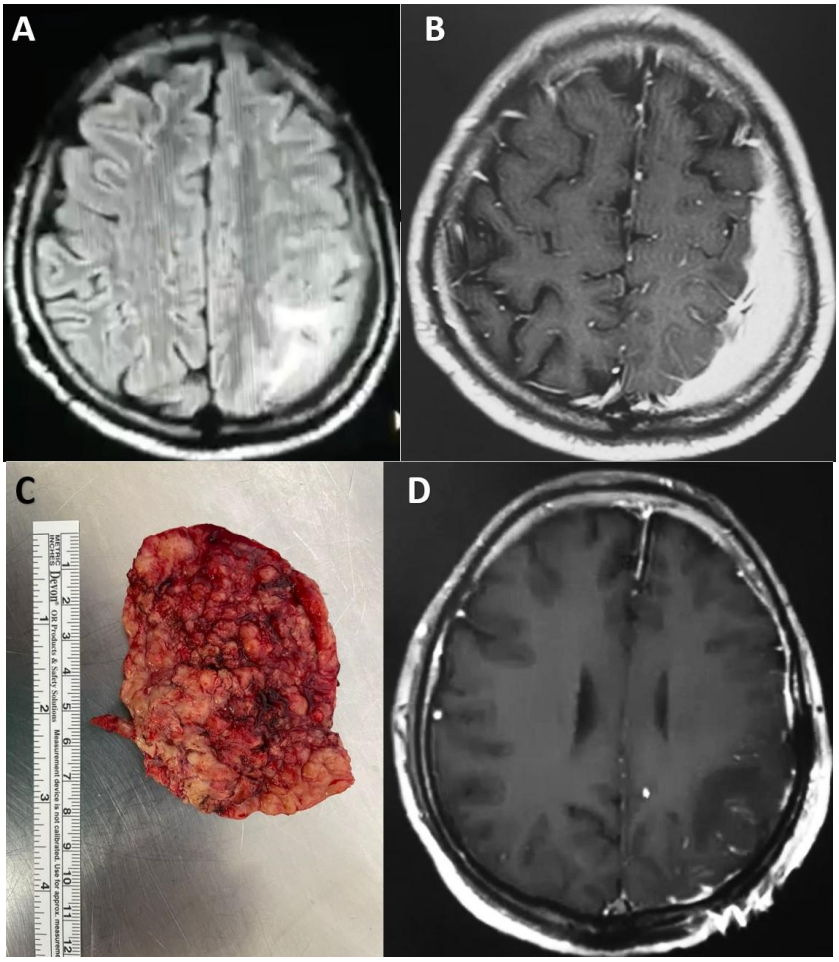

Figure 3. Imaging and operative features of intracranial Rosai-Dorfman disease.

(A) Axial FLAIR MRI showing an isointense left parietal dural-based lesion with surrounding vasogenic edema. (B) T1-weighted post-contrast MRI demonstrating homogeneous gadolinium enhancement of the lesion. (C) Gross image of the en-bloc resected dural-based mass (approximately 4.8 × 3.2 cm), displaying lobulated surface architecture. (D) Postoperative T1-weighted MRI with contrast confirming complete tumor resection and resolution of mass effect.

The patient underwent complete surgical resection via left parietal craniotomy. Intraoperatively, a firm, well-circumscribed dural-based mass was identified and removed en bloc (Figure 2C). Histopathological examination revealed the pathognomonic features of Rosai-Dorfman disease, including large histiocytes with abundant cytoplasm and characteristic emperipolesis—intact lymphocytes within the histiocytic cytoplasm. Immunohistochemical analysis confirmed S100 protein positivity and CD68 positivity, while CD1a was negative, consistent with the diagnosis of Rosai-Dorfman disease.

Comprehensive systemic evaluation including PET-CT imaging was unremarkable, confirming the localized nature of the disease. Postoperative imaging demonstrated complete tumor resection with resolution of mass effect (Figure 2D). The patient experienced immediate improvement in symptoms and remained recurrence-free at 2-year follow-up with complete neurological recovery.

While histopathological analysis was central to confirming the diagnosis of Rosai-Dorfman disease in this case, high-resolution photomicrographs of the resected specimen were not archived at sufficient quality for publication due to technical limitations at the time of tissue processing. Nevertheless, the diagnosis was confirmed by a certified neuropathologist based on the presence of emperipolesis and the classic immunoprofile (S100-positive, CD68-positive, CD1a-negative). All findings were documented in the institutional pathology report, and the case was reviewed in a multidisciplinary tumor board setting. Given the complete clinical, radiologic, surgical, and immunohistochemical correlation, we believe the case remains illustrative and diagnostically robust, even in the absence of published histology figures.

Case 3: Langerhans Cell Histiocytosis (L3 Vertebral Body)

A 36-year-old male presented with a 3-month history of progressive low back pain and right-sided sciatica following minor trauma during heavy lifting. The pain was described as constant, aching in quality, and progressively worsening despite conservative management. There was no associated fever, weight loss, or other systemic symptoms.

Computed tomography of the lumbar spine demonstrated a hyperdense lesion in the L3 vertebral body surrounded by a hypodense halo, with evidence of middle column fracture. Magnetic resonance imaging with intravenous contrast revealed a heterogeneously enhancing lesion involving the L3 vertebral body and right pedicle. The initial radiological impression was consistent with an atypical symptomatic hemangioma with pathological fracture. Radiological evaluation revealed characteristic features of a vertebral lesion suspicious for a pathological fracture and atypical neoplasm. These imaging findings are illustrated in Figure 4.

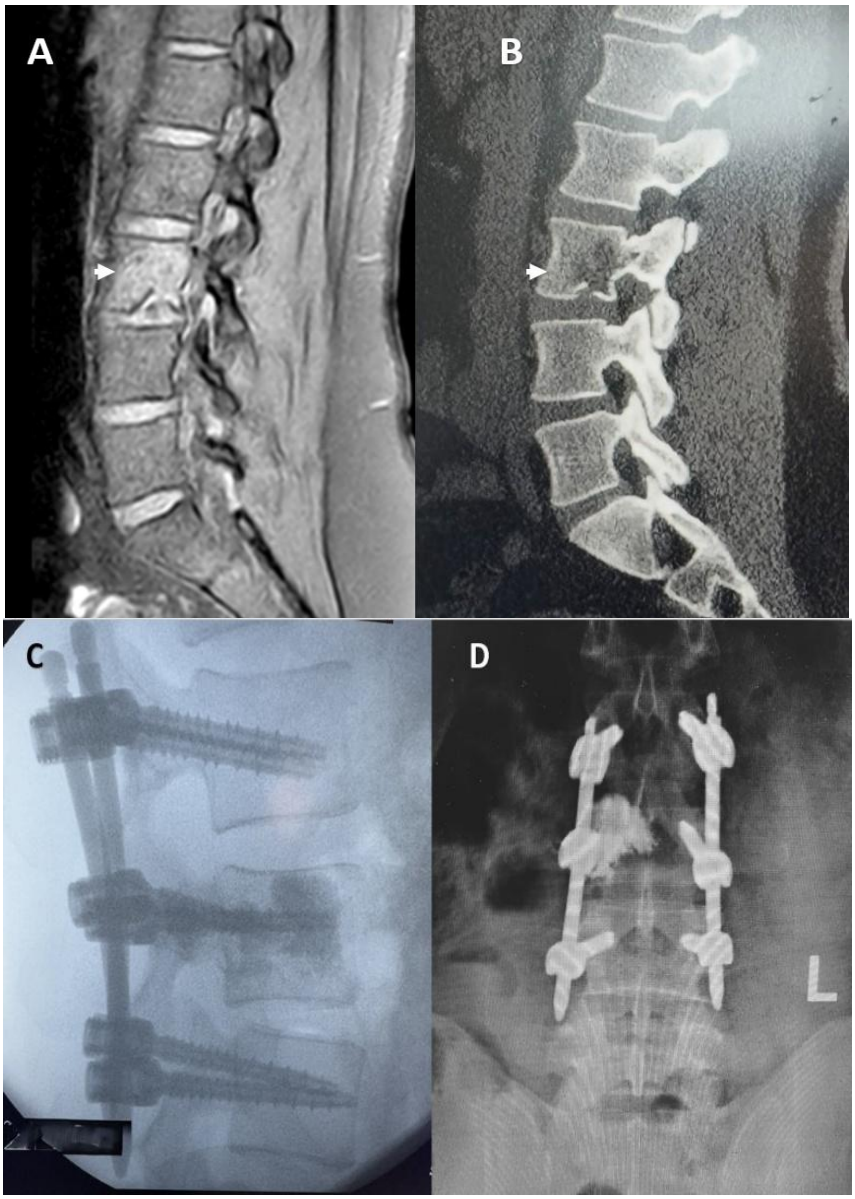

Figure 4. Imaging and postoperative findings of Langerhans cell histiocytosis involving the L3 vertebral body.

(A) Sagittal T1-weighted MRI with intravenous contrast demonstrates a heterogeneously enhancing lesion involving the L3 vertebral body and right pedicle. (B) Sagittal CT shows a hyperdense lesion in the right vertebral body surrounded by a hypodense halo. (C) Intraoperative lateral fluoroscopic image showing L2–L4 transpedicular screws and L3 vertebroplasty. (D) Postoperative anteroposterior radiograph confirming correct screw placement and cement augmentation at L3.

The patient underwent L2-L4 transpedicular screw fixation and L3 vertebroplasty. Intraoperative findings included friable bone with soft tissue extension, requiring tissue sampling for histopathological analysis. Microscopic examination revealed replacement of normal bone marrow architecture by collections of histiocyte-like cells intermixed with lymphocytes and spindle-shaped cells. Areas of necrosis, calcification, and hemorrhage were observed, along with mild cellular atypia.

Immunohistochemical analysis demonstrated positivity for CD1a, S100 protein, and CD68, establishing the diagnosis of Langerhans cell histiocytosis. Molecular analysis for BRAF V600E mutation was performed and was negative. Comprehensive systemic evaluation including PET scan was negative for evidence of multisystem involvement. The patient

remained asymptomatic at 12-month follow-up with no evidence of disease recurrence. Histopathological analysis confirmed the diagnosis of Langerhans cell histiocytosis, supported by distinct morphological and immunohistochemical features shown in Figure 5.

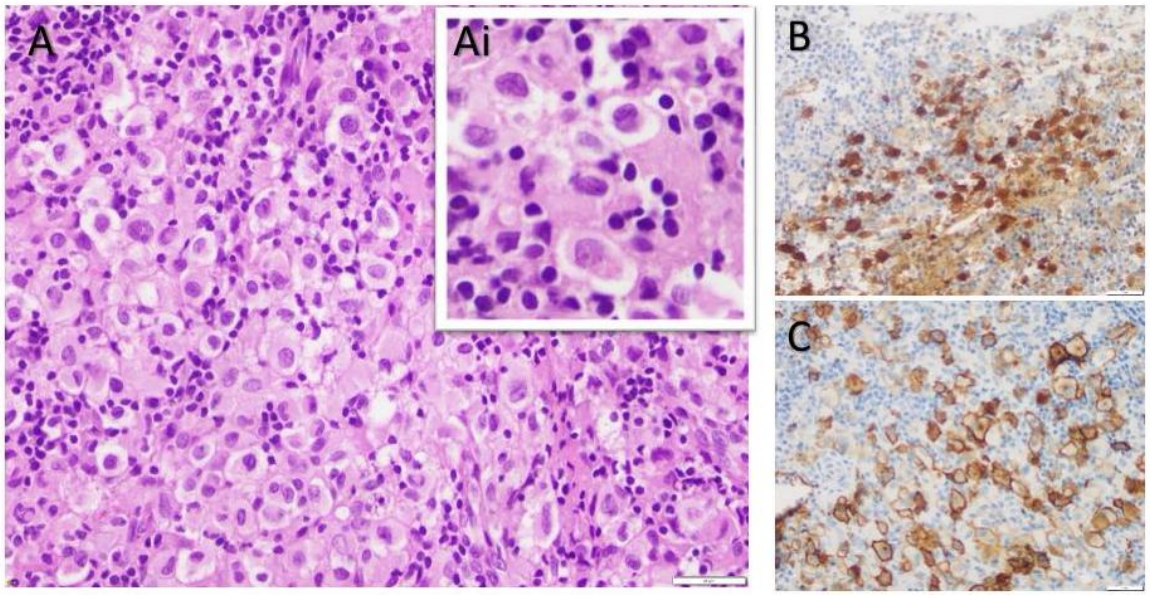

Figure 5. Histopathologic and immunohistochemical features of Langerhans cell histiocytosis (LCH).

(A) Hematoxylin and eosin (H&E) stain showing sheets of large histiocytic cells with abundant eosinophilic cytoplasm and convoluted, grooved nuclei, admixed with small lymphocytes (original magnification ×400).(Ai) High-power view highlights the characteristically twisted and grooved nuclei of Langerhans cells (H&E, ×1000).(B) Immunohistochemistry for S100 protein shows diffuse cytoplasmic nuclear staining in Langerhans cells; surrounding lymphocytes are negative (×400).(C) CD1a immunostaining highlights the membrane of Langerhans cells (×400).

To illustrate the diagnostic specificity and distinguishing features of each histiocytic subtype, Table1 summarizes the key clinical, histological, and molecular characteristics of the three cases, emphasizing the critical role of integrated immunohistochemical and molecular analysis in accurate subclassification.

Table 1. Summary of Histopathological and Immunohistochemical Findings

Case	Diagnosis	Age/Gender	Location	Key Histological Features	Immunohistochemistry	Molecular Findings
1	ALK+ Histiocytosis	27M	L3 nerve root	Foamy histiocytes, folded nuclei, Touton giant cells	ALK1^{+}, CD68^{+}, S100^{-}, CD1a^{-}	KIF5B-ALK fusion
2	Rosai-Dorfman	36M	Parietal dura	Large histiocytes with emperipolesis	S100^{+}, CD68^{+}, CD1a^{-}	Not performed
3	LCH	36M	L3 vertebra	Histiocyte-like cells, lymphocytes, necrosis	CD1a^{+}, S100^{+}, CD68^{+}	BRAF V600E negative

4. DISCUSSION

Histiocytic disorders involving the central nervous system and spine present significant diagnostic and therapeutic challenges due to their rarity and heterogeneous clinical behavior. This three-case series demonstrates the clinical and pathological spectrum of CNS-involved histiocytic disorders, including ALK-positive histiocytosis, Rosai-Dorfman disease, and Langerhans cell histiocytosis. Our findings emphasize the importance of integrating diagnostic modalities—morphological assessment, immunohistochemistry, and targeted molecular profiling—as essential tools for accurate subclassification, prognostication, and management.

4.1 Diagnostic Complexity and Clinical Implications

Central nervous system histiocytic disorders are diagnostically challenging entities whose clinical and radiological features overlap with those of more common CNS lesions, including meningiomas, schwannomas, and other dural-based tumors [1]. The recognition of rare histiocytic entities, particularly ALK-positive histiocytosis affecting spinal nerve roots, requires a high index of suspicion and comprehensive molecular testing [12]. Our ALK-positive case, initially misdiagnosed as a benign schwannoma, exemplifies the critical role of molecular diagnostics in accurate diagnosis. Surgical resection followed by molecular profiling revealed a KIF5B-ALK fusion, the molecular hallmark of ALK-positive histiocytosis. This finding aligns with previous reports demonstrating that identification of specific fusion proteins such as KIF5B-ALK can guide targeted therapy decisions [10,11,12].

Comprehensive molecular characterization of CNS histiocytic lesions, including ALK rearrangement and BRAF mutation analysis, should be performed as part of the diagnostic workup, particularly when conventional immunohistochemical markers yield inconclusive results [12]. This approach is essential when histological features overlap with other entities or when traditional markers such as CD1a and S100 are non-diagnostic [7]. Our experience demonstrates that the inclusion of molecular profiling in CNS histiocytic lesions results in accurate diagnosis and prevents potential misclassifications. These findings support the routine inclusion of ALK and BRAF testing in the immunohistochemical panel, especially for CNS histiocytic lesions negative for CD1a or S100.

4.2 Clinical Behavior and Therapeutic Strategies

The various histiocytic subtypes display variable biological behavior and clinical presentations. Langerhans cell histiocytosis demonstrates its characteristic predilection for skeletal involvement, affecting both axial spine and calvarial bones [2,3]. Our LCH case involving the L3 vertebral body in a 36-year-old male showed BRAF V600E-negative status, illustrating the molecular heterogeneity within LCH, as approximately 60% of cases harbor BRAF mutations [2,3]. The vertebral involvement required surgical stabilization, reflecting the potential for aggressive behavior in axial skeletal LCH, which may necessitate more intensive management compared to peripheral skeletal lesions [4,5].

ALK-positive histiocytosis represents a therapeutically actionable entity, with documented responses to ALK inhibitors such as crizotinib and ceritinib in systemic or recurrent disease [12]. Our localized case achieved excellent outcomes with surgical resection alone, demonstrating the efficacy of complete excision for localized disease. The Rosai-Dorfman case similarly showed excellent response to surgical resection, consistent with the generally benign behavior of this entity when affecting the CNS [6,7].

Our series emphasizes that therapeutic responses vary among histiocytosis subtypes, with treatment strategies requiring individualization based on histological subtype, anatomical location, and extent of disease involvement [6,13]. Complete surgical resection remains the mainstay of treatment for localized CNS histiocytic lesions when technically feasible, while systemic disease may require targeted therapies based on molecular alterations.

4.3 Radiologic and Pathologic Correlations

CNS histiocytic lesions frequently mimic other CNS pathologies on imaging, creating substantial diagnostic challenges. The Rosai-Dorfman case in our series presented as a dural-based lesion, radiologically resembling a convexity meningioma, a common presentation that can delay accurate diagnosis [6,7]. Similarly, the ALK-positive lesion at the L3 sensory nerve root was initially interpreted as a benign schwannoma, highlighting the diagnostic limitations of relying solely on radiological features [10,11].

Histopathological examination remains the cornerstone of diagnosis, with immunohistochemistry playing a critical role in confirming histiocytic origin and enabling accurate subclassification. The characteristic immunoprofiles—LCH ($CD1a^+$/$Langerin^+$/$S100^+$), RDD ($S100^+$/$CD1a^-$), and ALK-positive histiocytosis (ALK^+/$CD68^+$/$S100^-$/$CD1a^-$)—represent diagnostic hallmarks essential for accurate classification [1,6,11]. For ALK-positive histiocytosis, the identification of ALK expression combined with negative S100 and CD1a staining provides the immunohistochemical foundation for diagnosis. The subsequent discovery of the KIF5B-ALK fusion via RT-PCR provided definitive molecular confirmation, distinguishing this entity from other histiocytic disorders and nerve sheath tumors [11,12].

The importance of integrating imaging, histopathological, and molecular data is underscored by the risk of diagnostic error when relying on any single modality. Our series demonstrates that precise molecular characterization is necessary for

accurate subclassification and optimal treatment planning, particularly for CNS lesions where conventional imaging features frequently overlap [1,12].

4.4 Clinical Relevance of Molecular Profiling

Advances in molecular diagnostics have revolutionized the classification and management of histiocytic disorders. Molecular analyses targeting BRAF and ALK alterations provide not only diagnostic clarity but also therapeutic guidance for targeted therapy selection [2,8,12]. The identification of actionable molecular alterations has particular importance in the management of refractory or systemic disease, where targeted therapies have demonstrated significant efficacy.

The ALK-positive histiocytosis case in our series demonstrates the clinical utility of molecular characterization, where identification of the KIF5B-ALK fusion provided definitive diagnosis and established the potential for ALK-targeted therapy if systemic or recurrent disease were to develop [11,12]. While our patient achieved excellent outcomes with surgical resection alone, the availability of effective ALK inhibitors provides important therapeutic options for more extensive disease presentations.

Future studies should investigate the clinical effectiveness of ALK inhibitors in localized versus systemic ALK-positive histiocytosis to better inform therapeutic decision-making and establish optimal treatment algorithms for different disease presentations [12]. The development of predictive biomarkers for therapy response and the identification of resistance mechanisms will be important areas for future research.

4.5 Clinical Implications and Recommendations

Given the rarity and diagnostic complexity of CNS histiocytic disorders, a multidisciplinary approach incorporating neurosurgical, pathological, and molecular expertise is essential for optimal patient management. Routine inclusion of ALK and BRAF testing in immunohistochemical panels is strongly recommended for CNS histiocytic lesions, particularly when conventional markers are inconclusive or when histological features suggest a histiocytic proliferation [12,14]. Early molecular profiling can significantly aid in therapeutic planning, especially when actionable mutations are identified.

Our findings advocate for integrating comprehensive molecular diagnostics into routine clinical practice for atypical CNS presentations. Establishing standardized diagnostic protocols that incorporate advanced immunohistochemistry and genetic analysis will enhance diagnostic accuracy, minimize the risk of misclassification, and ultimately improve patient outcomes [1,14]. The development of institutional guidelines for the workup of suspected CNS histiocytic lesions, including specific recommendations for molecular testing, represents an important step toward optimizing the management of these rare but clinically significant entities.

To illustrate the diagnostic specificity and distinguishing features of each histiocytic subtype, Table 2 summarizes the key clinical, histological, and molecular characteristics of the three cases, emphasizing the critical role of integrated immunohistochemical and molecular analysis in accurate subclassification.

Table 21. Comparative Features of LCH, RDD, and ALK-Positive Histiocytosis Based on Current Literature

Feature	*LCH*	*RDD*	*ALK+ Histiocytosis*
Key markers	$CD1a^+$, $Langerin^+$, $S100^+$	$CD68^+$, $S100^+$, $CD1a^-$	$CD68^+$, ALK^+, $S100^-$, $CD1a^-$
Common sites	Bone, skin, pituitary	Lymph nodes, skin, CNS	Liver, CNS, skin, soft tissue
Molecular hallmark	BRAF V600E, MAPK mutations	Nonspecific	ALK fusions (e.g., KIF5B-ALK)
Prognosis	Good; variable by extent	Generally benign	Good if localized; systemic cases may vary
Treatment	Observation to chemotherapy	Observation, steroids, surgery	Surgery or ALK inhibitors (e.g., crizotinib)

5. CONCLUSION

This case-series highlights the diverse clinical, radiological, and molecular heterogeneity of CNS/spinal histiocytic disorders (e.g., LCH, RDD, ALK+ histiocytosis), which often overlap with other lesions, complicating diagnosis. Misclassification risks, exemplified by ALK+ histiocytosis mistaken for nerve sheath tumors due to atypical localization and insufficient IHC, underscore the necessity of integrating histology, targeted IHC (ALK/BRAF), and molecular profiling for precise classification. Surgical resection remains pivotal in management, with outcomes tied to accurate localization and histopathologic techniques. The study advocates routine ALK/BRAF testing in IHC panels to avoid diagnostic ambiguity, akin to somatic mutation profiling in precision medicine. Multicenter collaboration is critical to pooling rare cases, enabling

robust statistical analyses, outcome modeling, and standardized diagnostic/molecular protocols. Understanding cellular/molecular behavior of these disorders is essential for advancing characterization and therapeutic strategies, emphasizing the evolving role of molecular diagnostics in CNS/spinal histiocytosis.

REFERENCES

[1] Emile JF, Abla O, Fraitag S, et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood. 2016;127(22):2672–2681. https://doi.org/10.1182/blood-2016-01-690636

[2] Badalian-Very G, Vergilio JA, Degar BA, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood. 2010;116(11):1919–1923. https://doi.org/10.1182/blood-2010-04-279539

[3] Berres ML, Lim KP, Peters T, et al. BRAF-V600E expression in precursor versus differentiated dendritic cells defines clinically distinct LCH risk groups. J Exp Med. 2014;211(4):669–683. https://doi.org/10.1084/jem.20130977

[4] Grois N, Prayer D, Prosch H, et al. Course and clinical impact of MRI findings in diabetes insipidus associated with Langerhans cell histiocytosis. Pediatr Blood Cancer. 2004;43(3):248–252. https://doi.org/10.1002/pbc.20161

[5] Rodriguez-Galindo C, Allen CE. Langerhans cell histiocytosis. Blood. 2020;135(16):1319–1331. https://doi.org/10.1182/blood.2019000932

[6] Abla O, Jacobsen E, Picarsic J, et al. Consensus recommendations for the diagnosis and clinical management of Rosai-Dorfman-Destombes disease. Blood. 2018;131(26):2877–2890. https://doi.org/10.1182/blood-2018-03-839753

[7] Dalia S, Sagatys E, Sokol L, Kubal T. Rosai-Dorfman disease: tumor biology, clinical features, pathology, and treatment. Cancer Control. 2014;21(4):322–327. https://doi.org/10.1177/107327481402100405

[8] Haroche J, Charlotte F, Arnaud L, et al. High prevalence of BRAF V600E mutations in Erdheim-Chester disease but not in other non-Langerhans cell histiocytoses. Blood. 2012;120(13):2700–2703. https://doi.org/10.1182/blood-2012-05-430140

[9] Diamond EL, Durham BH, Haroche J, et al. Diverse and targetable kinase alterations drive histiocytic neoplasms. Cancer Discov. 2016;6(2):154–165. https://doi.org/10.1158/2159-8290.CD-15-0745

[10] Chan JK, Lamant L, Algar E, et al. ALK+ histiocytosis: a novel type of systemic histiocytic proliferative disorder of early infancy. Blood. 2008;112(7):2965–2968. https://doi.org/10.1182/blood-2008-03-145698

[11] Chang KTE, Tay AZE, Kuick CH, et al. ALK-positive histiocytosis: an expanded clinicopathologic spectrum and frequent presence of KIF5B-ALK fusion. Mod Pathol. 2019;32(4):598–608. https://doi.org/10.1038/s41379-018-0168-6

[12] Kemps PG, Picarsic J, Durham BH, et al. ALK-positive histiocytosis: a new clinicopathologic spectrum highlighting neurologic involvement and responses to ALK inhibition. Blood. 2022;139(2):256–280. https://doi.org/10.1182/blood.2021013338

[13] Goyal G, Young JR, Koster MJ, et al. The Mayo Clinic Histiocytosis Working Group consensus statement for the diagnosis and management of Langerhans cell histiocytosis in adults. Mayo Clin Proc. 2019;94(10):2054–2071. https://doi.org/10.1016/j.mayocp.2019.02.031

[14] Jaber OI, Al Jarrah D, Hiasat M, Al Hussaini M. ALK-positive histiocytosis: a case report and literature review. Turk J Pathol. 2020;36(3):230–236. https://doi.org/10.5146/tjpath.2020.01507