CASE REPORT

Orbital Anaplastic Lymphoma Kinase-Positive Histiocytosis in an Adult: A Rare Isolated Manifestation

Norlisa Khalid[1,2], Noraini Mohamad[1], Amizatul Aini Salleh[1], Shau-Kong Lai[2], Huzlinda Hussin[2]

[1] Department of Pathology, Hospital Sultan Idris Shah, Jalan Puchong, 43000 Kajang, Selangor, Malaysia
[2] Department of Pathology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia

ABSTRACT

ALK-positive histiocytosis is a rare histiocytic neoplasm driven by *ALK* gene rearrangements, most described in infants with systemic involvement. Recent literature has expanded its spectrum to include localised disease in older patients. To the best of our knowledge, this is the first reported case of isolated orbital *ALK*-positive histiocytosis in an adult. We present a unique case of a 28-year-old male with acute-onset diplopia, blurred vision, and right eye ptosis. Imaging revealed a well-defined extraconal mass in the right orbit. Surgical excision was performed, and histopathological examination revealed atypical histiocytes with inflammatory infiltrates. Immunohistochemistry showed strong positivity for ALK-1 and CD68, confirming *ALK*-positive histiocytosis. The case posed significant diagnostic challenges due to features that overlapped with other histiocytic and inflammatory conditions. This report expands the known clinical and anatomical spectrum of *ALK*-positive histiocytosis and highlights the importance of thorough diagnostic evaluation and the effectiveness of surgical management in localised disease.

Malaysian Journal of Medicine and Health Sciences (2025) 21(SUPP12):130-133. doi:10.47836/mjmhs.21.s12.24

Keywords: *ALK* Kinase, Anaplastic Lymphoma Kinase, Histiocytosis, Orbital neoplasms, Gene fusion

Corresponding Author:
Huzlinda Hussin, MD, MPath
Email: huzlinda@upm.edu.my
Tel:+60397692781

INTRODUCTION

Anaplastic lymphoma kinase (*ALK*)-positive histiocytosis is a rare neoplastic disorder of the histiocytic lineage characterised by ALK immunoreactivity due to *ALK* gene rearrangement, leading to clonal proliferation of histiocytes with distinct morphological and immunophenotypic features (1). Recent molecular advances have elucidated the oncogenic role of *ALK* gene fusions, not only as a diagnostic hallmark but also as a potential therapeutic target, particularly in disseminated or refractory cases (1). This condition typically presents with multisystem involvement, notably affecting the liver, spleen, bone marrow, and central nervous system, especially in infants (2). However, isolated or localised forms have been increasingly recognised in adults, with reported involvement of the nervous system, skin, soft tissues, and breast (1,2).

Orbital involvement is exceedingly rare, with only a single periorbital (eyelid) case reported (3). No cases of true isolated orbital involvement in adults have been documented, underscoring the novelty of the present case. The clinical presentation of orbital lesions can be challenging due to substantial overlap with other histiocytic disorders, such as Erdheim- Chester disease (ECD), Juvenile xanthogranuloma (JXG), Rosai-Dorfman disease (RDD) and Langerhans cell histiocytosis (LCH), which may exhibit overlapping histopathological features (2,4). For example, RDD is often associated with emperipolesis and strong S100 positivity, LCH typically shows CD1a expression and nuclear grooves, ECD is characterised by foamy histiocytes often with *BRAF* mutations, while JXG usually presents with Touton giant cells but lacks ALK expression (2,4). Accurate diagnosis

classification is clinically important because treatment strategies and prognosis differ significantly. While systemic *ALK*-positive histiocytosis has shown robust responses to ALK inhibitors such as critozitinib, alectinib and brigiatinib, localised lesions are usually managed surgically (2). Prognostic implications and recurrence risks also vary significantly, further underscoring the importance of precise diagnostic stratification.

Here, we present the first case of isolated orbital *ALK*-positive histiocytosis in an adult. Most reported cases of *ALK*-positive histiocytosis have involved the central nervous system, liver, spleen, bone marrow, breast, skin, and soft tissues (1,2,4,5). By documenting this novel orbital site, our case expands the known clinical and anatomical spectrum of *ALK*-positive histiocytosis and highlights the importance of considering this entity in the differential diagnosis of orbital lesions.

CASE REPORT

A 28-year-old male with no significant medical history presented with a one-month history of painless right eye protrusion. The symptoms were progressively worsened. He then developed acute-onset diplopia, blurred vision, and right eyelid ptosis 5 days prior to admission. On physical examination, proptosis of the right eye and limited upward gaze were observed. Neurological examination was unremarkable, with no focal deficits identified. No signs of systemic involvement, such as lymphadenopathy, hepatosplenomegaly, or skin lesions, were present. A contrast-enhanced computed tomography (CT) scan of the orbit revealed a well-defined, 2.5 x 1.8 cm extraconal mass in the superotemporal region of the right orbit. The mass compressed the right globe but was well delineated from adjacent orbital structures. It showed homogeneous enhancement without evidence of bony involvement or adjacent tissue infiltration (Fig.1A). Two weeks later, the right extraconal mass was surgically excised.

Macroscopic examination of the excised mass revealed a well-circumscribed lesion with a whitish-yellow cut surface. Microscopic analysis showed that the tumour was primarily composed of histiocytic cells with a mixture of large epithelioid, foamy and spindle cell morphology. These cells exhibited irregular nuclear contours, open chromatin, prominent nucleoli, and abundant eosinophilic cytoplasm with indistinct borders. The lesion was surrounded by a dense inflammatory infiltrate composed of small lymphocytes, plasma cells, and eosinophils. Emperipolesis was observed, a finding classically associated with RDD, although not specific to it. Mitoses were rare, and no necrosis was identified (Fig. 1B-D). Extensive immunohistochemical study for lymphoma markers, including CD45, CD3, CD5, CD20, CD79a, and PAX5, was negative, ruling out lymphoma. Immunohistochemical analysis confirmed the diagnosis of *ALK*-positive histiocytosis. The histiocytes were strongly positive for CD68, confirming a histiocytic origin. Immunostaining for ALK-1 showed strong granular cytoplasmic and membranous staining, characteristic of *ALK*-positive histiocytosis. Staining for S100 and CD1a were negative, excluding LCH and RDD. Ki-67 staining revealed a proliferative index of approximately 5%, suggesting a relatively indolent course. The absence of myofibroblastic markers, such as smooth muscle actin (SMA), further differentiated this entity from inflammatory myofibroblastic tumours (IMT). The summary of the relevant immunohistochemical study findings are summarised in Table I and the staining

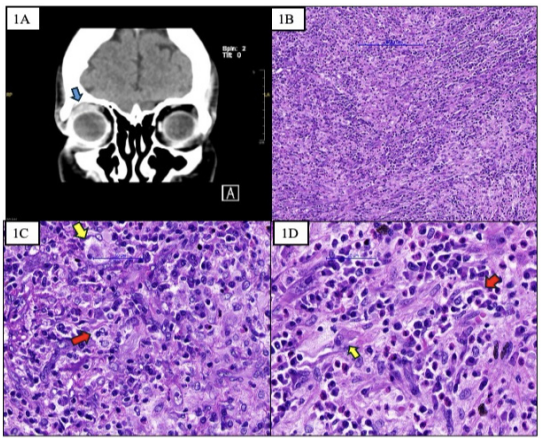

Fig 1A-D show the radiological and histopathological features of isolated orbital ALK-positive histiocytosis. 1A: Coronal CT scan of the orbit reveals a well-defined extraconal soft tissue mass in the superotemporal quadrant of the right orbit (blue arrow), exerting pressure on the globe. 1B: Low-power photomicrograph (H&E, 100Ч) showing a cellular lesion composed of large epithelioid, foamy, and spindle-shaped histiocytic cells surrounded by a dense inflammatory infiltrate. 1C&1D: High-power photomicrographs (H&E, 400×) demonstrating histiocytic cells with irregular nuclear contours, open chromatin, some prominent nucleoli, and abundant eosinophilic to clear cytoplasm with indistinct borders (yellow arrow). The background contains small lymphocytes, plasma cells, eosinophils, and scattered emperipolesis (red arrow)

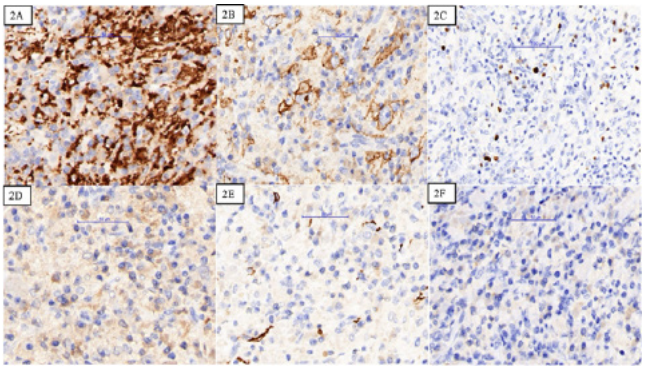

Fig. 2A-F (400X magnification) show immunohistochemical features of the orbital lesion, confirming the diagnosis of ALK-positive histiocytosis. 2A: CD68 highlights the histiocytic lineage with diffuse strong cytoplasmic positivity. 2B: ALK-1 immunostaining shows strong granular cytoplasmic and membranous positivity in lesional histiocytes. 2C: Ki-67 immunostaining demonstrates a low proliferative index. 2D: S100 is negative for cytoplasmic staining , thereby excluding Rosai-Dorfman disease. For Langerhans cell histiocytosis typically shows both nuclear and cytoplasmic S100 positivity. Notably, this image demonstrated high background staining for S100 which should carefully interpreted. 2E: SMA (smooth muscle actin) is negative for cytoplasmic staining, ruling out myofibroblastic differentiation. 2F: CD1a is negative for membranous staining, excluding Langerhans cell histiocytosis.

Table I: Summary of immunohistochemical study findings

Immunohistochemical marker	Results and interpretation
CD 68	Positive – supports histiocytic disease in origin
ALK-1	Positive - strong granular cytoplasmic staining, characteristics of *ALK*-positive histiocytosis
S100 and CD1a	Negative - Langerhans cell histiocytosis and and Rosai- Dorfman Disease excluded
SMA (Smooth muscle actin)	Negative – Inflammatory myofibroblastic tumour excluded

images are presented in Fig. 2A-F.

The patient underwent a complete surgical excision of the orbital lesion. However, two weeks post-operatively, he developed acute third and sixth cranial nerve palsies. A CT scan revealed a fusiform aneurysm involving the right internal carotid artery. The cranial nerve palsies may have resulted from either surgical manipulation or compression by the aneurysm. It remains uncertain whether the aneurysm was tumour-related or a surgical complication. He was subsequently referred to a tertiary neurological referral centre for further evaluation and management. As the patient continued follow-up at the referral centre, no further clinical updates were available from our institution, and long-term follow-up could not be ascertained.

DISCUSSION

ALK-positive histiocytosis was first described by Chan et al. in 2008, based on cases in infants with multisystem involvement, including hepatomegaly, thrombocytopenia and diffuse histiocytic infiltration (1,2). Since then, the clinical spectrum has expanded to include adult-onset and localised forms involving diverse anatomical sites, such as central nervous system, skin, breast, and soft tissue (2,5). The 5th edition of WHO Classification of Haematolymphoid Tumours categorises *ALK*-positive histiocytosis into three major groups: multisystem disease in infants, multisystem involvement in other age groups, and disease limited to a single organ system (1). Our case contributes to this spectrum by reporting isolated orbital involvement, an extremely rare presentation not previously documented in adults.

Histologically, *ALK*-positive histiocytosis demonstrates variable morphology with lesional cells displaying epithelioid, foamy, and spindle cell forms, often accompanied by a dense mixed inflammatory infiltrate (4). Our case revealed emperipolesis, but this finding, like Touton giant cells, is not pathognomonic and may also occur in RDD, JXG, and ECD (2,4). In evaluating the differential diagnoses, LCH was initially considered due to patient's age and orbital involvement. *BRAF* V600E mutations are reported in over 50% of LCH cases, and testing can provide additional diagnostic certainty (1,2). In our case, BRAF testing was not performed, which represents a limitation. Nevertheless, the absence of CD1a expression and the strong ALK positivity make LCH unlikely.

Rosai-Dorfman disease can also involve the orbit. However, classic RDD histiocytes exhibit abundant pale cytoplasm, large round nuclei and S100 positivity without ALK expression (1,4). In contrast, our case showed ALK-1 positivity with a granular cytoplasmic pattern, with no significant S100 and cyclin D1 expression, making RDD`improbable. In the study by Kemps et al. (2022), approximately 50% of ALK-histiocytic cases demonstrated histologic characteristics resembling RDD, such as S100 positivity and evidence of emperipolesis. The histiocytic cells were also positive for OCT-2, pERK, and Cyclin D1 expression (2). Additionally, they found that four out of 39 cases displayed focal weak ALK staining, while three showed an exclusive cytoplasmic Golgi dot-like staining pattern, which could be interpreted as negative (2). These findings further highlight the challenges in differentiating between RDD and *ALK*-positive histiocytosis. Clinically, RDD may be self-limiting or responsive to corticosteroids, unlike *ALK*-positive histiocytosis which may require surgical or targeted therapy.

ECD is a systemic histiocytic proliferation characterised by foamy histiocytes with small nuclei and typically affect older individual (4,5). Unlike our case, ECD frequently involves long bones, retroperitoneum and cardiovascular structures (5). *BRAF* mutations are also common in ECD, and testing for *BRAF* or related

Table II: Immunohistochemical and molecular studies of ALK-positive histiocytosis comparing with other histiocytic disorders.

		ALK-positive histiocytosis	RDD	LCH	ECD	JXG
Immunohistochemical marker	CD 68	+	+	+	+	+
	ALK	+ (granular cytoplasmic)	-	-	-	-
	S100	-/weak +	+	+	-/weak +	Usually -
	CD1a	-	-	+	-	-
Molecular	*ALK* gene fusions	Identified (Most common: *KIF-5B::ALK* fusion)	Lack	Lack (Has *BRAF* V600E mutation)	Lack (Has *BRAF* V600E mutation)	Lack

RDD = Rosai–Dorfman disease; LCH = Langerhans cell histiocytosis; ECD = Erdheim–Chester disease; JXG = Juvenile xanthogranuloma

mutations supports the diagnosis and guides therapy with BRAF inhibitors (1,5). However, the clinical presentation and ALK immunoreactivity make ECD less probable. JXG, while morphologically similar, primarily affects children and exhibits CD68 positivity without *ALK* expression (1). Table II simplified the immunohistochemical and molecular findings of *ALK*-positive histiocytosis and other differential diagnoses of histiocytic disorders.

IMT was also considered, especially given the presence of spindle cells and ALK positivity. However, IMT typically shows myofibroblastic differentiation with expression of SMA or desmin, neither of which were detected in this case. Moreover, strong histiocytic marker expression (CD68) and the absence of myofibroblastic features exclude IMT. While rare reports such as those by Kashima et al. (2020) have described *ALK*-positive spindle cell tumours with overlapping morphology and SMA expression, definitive diagnosis in such cases relies on molecular confirmation of fusion partners such as kinesin family member 5B (*KIF5B::ALK*), which is frequently found in *ALK*-positive histiocytosis (2,4,5). Histiocytic sarcoma, a malignant counterpart, is typically distinguished by pronounced nuclear pleomorphism, elevated mitotic activity, necrosis, and lack of ALK expression, which are inconsistent with this case (1). The low Ki-67 index, in this case, also supports a relatively indolent behaviour inconsistent with histiocytic sarcoma.

Molecularly, *ALK*-positive histiocytosis is defined by rearrangements involving the *ALK* gene, with *KIF5B::ALK* identified as the most frequent fusion in recent studies (2,5). Other fusion partners, such as tropomyosin 3 (TPM3), clathrin heavy chain (CLTC), tropomyosin-receptor kinase fused gene (TFG), and echinoderm microtubule-associated protein-like 4 (EML4), have also been reported (2,4,5). Although molecular confirmation of the ALK fusion partner was not performed in this patient, the characteristic morphology and strong ALK immunoreactivity provide sufficient diagnostic confidence under current WHO criteria, and the absence of molecular testing would not have altered clinical management in this localised case (1). Recognition of *ALK* rearrangements not only aids diagnosis but also provides a rationale for targeted therapy. Isolated orbital *ALK*-positive histiocytosis has not previously reported in adults, making this case a novel addition to the disease spectrum. The case emphasises that localised orbital disease can be managed surgically, whereas systemic cases may require ALK-inhibitor therapy.

CONCLUSION

This case highlights the diagnostic complexity of *ALK*-positive histiocytosis, particularly in unusual anatomical sites. Integrating clinical, radiological, histopathological, and immunophenotypic data is essential in distinguishing this entity from morphologically and immunophenotypically overlapping histiocytic and myofibroblastic disorders. Notably, it represents the first reported isolated orbital involvement in an adult, adding a novel contribution to the limited literature and underscoring the importance of precise diagnosis for guiding therapy.

ACKNOWLEDGEMENT

The authors would like to thank the Department of Pathology, Hospital Sultan Idris Shah, Serdang, Selangor, Malaysia, for its support in preparing this case report.

REFERENCE

1. Coupland SE, Chan J, Yoshida A, Jean-Franɜois, Picarsic J, Kenneth Tou En. WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. [Internet]. 5th ed. Lyon (France): International Agency for Research on Cancer; 2024. (WHO classification of tumours series; vol. 11). Available from: https://tumourclassification.iarc.who.int/chapters/63.
2. Kemps PG, Picarsic J, Durham BH, Нйlias-Rodzewicz Z, Hiemcke-Jiwa L, van den Bos C, et al. ALK-positive histiocytosis: a new clinicopathologic spectrum highlighting neurologic involvement and responses to ALK inhibition. Blood. 2022 Jan 13;139(2):256–80.
3. Lin MJ, Kuo KT, Liao SL, Wei YH. Anaplastic lymphoma kinase-positive histiocytosis with periorbital involvement: a novel presentation. Can J Ophthalmol. 2025 Feb 1;60(1):e165–7.
4. Zou L, Lu T, Li M, Wang A, Zhang Z, Pan B, et al. Localised ALK-positive histiocytosis in lung with EML4::ALK fusion. Pathology (Phila). 2024 June 1;56(4):604–6.
5. Liu W, Liu H jie, Wang W ya, Tang Y, Zhao S, Zhang W yan, et al. Multisystem ALK-positive histiocytosis: a multi-case study and literature review. Orphanet J Rare Dis. 2023 Mar 13;18(1):53.