Epithelioid fibrous histiocytoma of eyelid in children: A case report

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Received January 21, 2026; Accepted April 21, 2026

DOI: 10.3892/etm.2026.13203

Abstract. A 7-year-old male patient presented to Jinan Mingshui Eye Hospital (Jinan, China) in June 2025 with a 3-month history of a progressively enlarging mass on the right upper eyelid. The lesion was asymptomatic, with no associated pain, redness or discharge. Physical examination revealed a well-defined, smooth, yellow-red, round mass measuring ~6x5x5 mm at the medial canthus of the right upper eyelid, adjacent to the upper lacrimal punctum. Under general anesthesia, the tumor was completely excised in June 2025. Histopathological examination showed squamous epithelium overlying proliferations of small spindle cells, mitotic figures and scattered Touton-like giant cells. Immunohistochemistry revealed positive staining for CD68, CD163, S-100, CD1a, CD10 and anaplastic lymphoma kinase (ALK), with a Ki-67 proliferation index of ~10%. A diagnosis of ALK-positive epithelioid fibrous histiocytoma (EFH) was established. Postoperative recovery was uneventful, with no recurrence observed during a 6-month follow-up period. This case highlights an unusual presentation of EFH in a pediatric eyelid, where a rare tumor that occurred in the eyelid of a 7-year-old child was accurately diagnosed through a set of immunohistochemical panels containing tissue cell markers (CD68 and CD163), melanoma cell markers (S-100), dendritic cell markers (CD1a), mesenchymal cell markers (CD10) and ALK.

Introduction

Epithelioid fibrous histiocytoma (EFH), also referred to as epithelioid cell histiocytoma, is an uncommon benign mesenchymal tumor of the skin that was first described by Jones *et al* in 1989 (1). As a distinct entity within the spectrum of cutaneous fibrous histiocytic lesions, EFH has garnered increasing attention due to its unique clinicopathological features and distinctive molecular signature. Clinically, it typically presents as a solitary, slow-growing red to reddish-brown nodule or plaque, usually measuring <2 cm in diameter (1,2). The tumor occurs predominantly on the lower extremities of young-to-middle-aged adults, with a mean age of 42 years and a slight female predominance (1,2). Despite its generally characteristic presentation, EFH remains underrecognized in clinical practice, particularly when it occurs in atypical locations or in unusual age groups.

Histopathologically, EFH is characterized by a dermal-based proliferation of large, rounded epithelioid cells, often arranged in nested or sheet-like patterns. These cells exhibit abundant eosinophilic cytoplasm, vesicular nuclei and distinct cell borders. Overlying epidermal hyperplasia is frequently observed, which can mimic melanocytic or epithelial neoplasms and contribute to diagnostic confusion. For numerous years, EFH was considered merely a variant of conventional benign fibrous histiocytoma (BFH); however, advances in molecular pathology have fundamentally revised this understanding. A landmark discovery was the identification of recurrent anaplastic lymphoma kinase (ALK) gene rearrangements in EFH, most commonly involving fusion partners such as sequestosome 1 and vinculin (VCL) (2-4). These rearrangements lead to constitutive activation of the ALK receptor tyrosine kinase and subsequent ALK protein overexpression, which can be reliably detected by immunohistochemistry (2-4). Notably, conventional BFH consistently lacks ALK expression, rendering ALK immunohistochemistry a highly sensitive and specific diagnostic marker for distinguishing EFH from its histologic mimics.

The accurate diagnosis of EFH relies heavily on a panel of immunohistochemical biomarkers, each serving to exclude specific entities in the differential diagnosis. CD68 and CD163 are histiocytic markers that indicate a histiocytic lineage, commonly positive in EFH but also expressed in juvenile xanthogranuloma and other histiocytic disorders. S-100 is a marker of melanocytic and neural differentiation; its expression in EFH can lead to potential confusion with Spitz nevus or melanoma (5). CD1a is a classic marker for Langerhans cell histiocytosis, and its occasional expression in EFH necessitates careful differentiation from dendritic cell neoplasms. CD10, a

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Key words: epithelioid fibrous histiocytoma, eyelid tumor, pediatric, anaplastic lymphoma kinase, immunohistochemistry

mesenchymal and germinal center marker, may be positive in a subset of EFH and helps distinguish it from other spindle cell lesions. Most importantly, ALK immunohistochemistry serves as a key diagnostic tool, as ALK overexpression due to underlying gene rearrangements is a highly specific feature of EFH that reliably distinguishes it from its histologic mimics, all of which are consistently ALK-negative (2). The diagnostic utility of these markers lies not in any single positive result, but in the comprehensive staining profile when interpreted in conjunction with histomorphology.

Although EFH is classically considered a tumor occurring in young to middle-aged adults, rare cases have been documented in atypical anatomical locations, including the eyelids, nasal region, oral cavity and other areas of the head and neck (3). Furthermore, sporadic reports have extended the age range of affected individuals to include children and the elderly (5). Such atypical presentations pose significant diagnostic challenges, as the differential diagnosis expands to encompass a variety of benign and malignant entities more commonly encountered in these locations, including Spitz nevi, juvenile xanthogranuloma, pilomatrixoma, basal cell carcinoma and various adnexal tumors. In such cases, histopathological evaluation alone may be insufficient, and ancillary studies-particularly ALK immunohistochemistry-are essential for establishing an accurate diagnosis (6,7).

In the present study, a rare case of ALK-positive EFH occurring in the eyelid of a 7-year-old male patient was documented. To the best of our knowledge, the occurrence of EFH in this demographic-a prepubertal child- and at this specific periocular location has been seldom described in the literature (8). This case not only expands the known clinical spectrum of EFH but also underscores the importance of considering this entity in the differential diagnosis of cutaneous nodules in children and at atypical anatomical sites. Furthermore, it highlights the critical role of molecular ancillary testing in achieving a correct diagnosis, thereby preventing unnecessary overtreatment or misdiagnosis. Given the benign nature of EFH and its excellent prognosis following complete local excision, accurate recognition of this entity carries important clinical implications.

Case report

A 7-year-old male patient was referred to Jinan Mingshui Eye Hospital outpatient department (Jinan, China) in June 2025, for the evaluation of a slowly growing mass on the right upper eyelid, which had been present for 3 months. The lesion was asymptomatic, with no history of trauma, inflammation or visual disturbance. Systemic review and family history revealed unremarkable results. Ophthalmic examination revealed a yellow-red, round, well-circumscribed mass at the medial canthus of the right upper eyelid, near the upper lacrimal punctum, measuring 6x5x5 mm (Fig. 1A). The surface was smooth and intact, with no tenderness or involvement of the lacrimal punctum. The bulbar conjunctiva, cornea and fundus were normal. Surgical excision was performed under general anesthesia 4 days later in June 2025. The operation was performed under general anesthesia and surgical microscope. A tear point probe was placed in the upper tear point to identify and protect the tear point (Fig. 1B). Subsequently, fine micro-scissors were used to perform sharp separation along the outside of the tumor capsule, where the tumor was completely removed without damaging the lacrimal point during the operation (Fig. 1C). Due to the small size of the tumor and clinical consideration of it being benign, to reduce the operation time, no intraoperative frozen section examination was performed. The final status of the surgical margin was confirmed by postoperative paraffin pathological evaluation (data not shown). Microscopic examination revealed squamous epithelium overlying a dense proliferation of small spindle cells, with occasional mitotic figures and scattered Touton-like giant cells (Fig. 1D and E). Immunohistochemical staining showed partial positivity for CD68, CD163, S-100, CD1a and CD10, along with cytoplasmic ALK expression (Fig. 1F-K). The Ki-67 labeling index was ~10% (Fig. 1L). Based on these findings, a diagnosis of ALK-positive EFH was confirmed. The patient was followed up 9 days after surgery in June 2025, at which time the surgical site was well-healed, with no signs of inflammation or recurrence (Fig. 1M). The patient was followed up at 1, 3 and 6 months postoperatively. At each visit, clinical examination of the surgical site revealed no evidence of local recurrence, and the patient remained asymptomatic. No recurrence was observed during the 6-month follow-up period.

Materials and methods

Tissue processing and histopathological examination. The excised tumor specimen was immediately fixed in 10% neutral-buffered formalin for 24 h at room temperature. Following fixation, the tissue was routinely dehydrated, cleared, embedded in paraffin wax and sectioned at a thickness of 4 μm. Sections were stained with hematoxylin and eosin for routine histopathological evaluation. All histopathological examinations were performed under a light microscope (Olympus BX53; Olympus Corporation) by two experienced pathologists independently.

Immunohistochemistry. Immunohistochemical staining was performed on 4-μm-thick paraffin sections using the EnVision FLEX polymer detection system (Dako; Agilent Technologies, Inc.). In brief, sections were deparaffinized in xylene and rehydrated through a graded ethanol series. Antigen retrieval was performed by heating the sections in EDTA buffer (pH 8.0) using a pressure cooker for 2.5 min at 121˚C, followed by cooling to room temperature. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide for 10 min. The sections were then incubated with primary antibodies at 4˚C overnight. The following primary antibodies were used: Anti-CD68 (dilution, 1:200; cat. no. M0814; Dako; Agilent Technologies, Inc.), anti-CD163 (dilution, 1:200; cat. no. M0892; Dako), anti-S-100 (polyclonal; dilution, 1:500; cat. no. Z0311; Dako), anti-CD1a (dilution, 1:50; cat. no. M3571; Dako), anti-CD10 (dilution, 1:100; cat. no. M7302; Dako), anti-ALK (dilution, 1:100; cat. no. 3633; Cell Signaling Technology, Inc.) and anti-Ki-67 (dilution, 1:100; cat. no. M7240; Dako). After washing with PBS, sections were incubated with reagents from the EnVision FLEX polymer detection system (Dako) for 30 min at room temperature. The reaction was visualized with 3,3'-diaminobenzidine chromogen and sections were counterstained with hematoxylin.

Positive controls included known ALK-positive anaplastic large cell lymphoma tissue provided by an external collaborating institution, Jinan KingMed Diagnostics Co., Ltd. (Jinan,

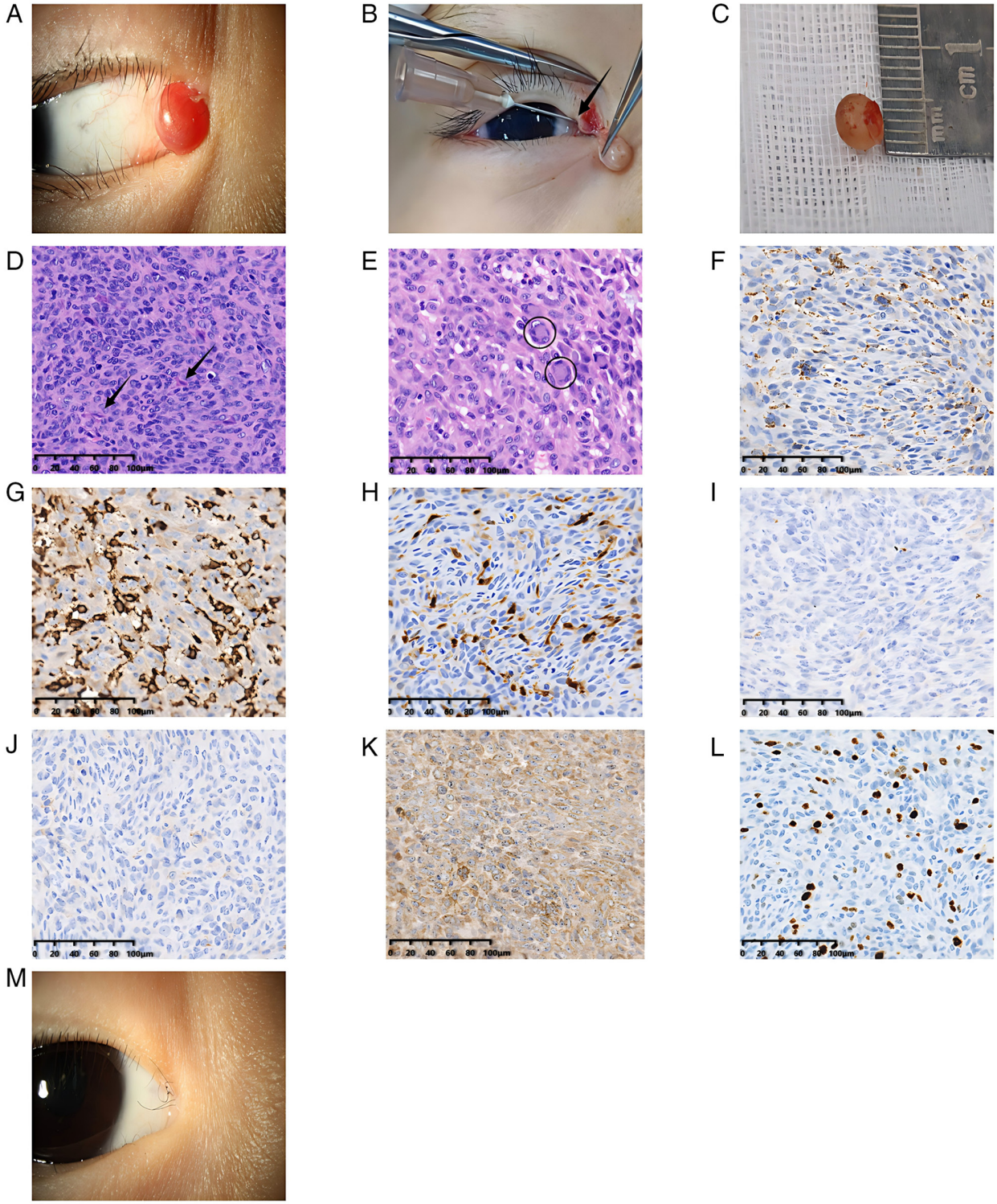

Figure 1. Clinical and pathological features of adjoining masses in the right eye. (A) Preoperative appearance reveals a clear boundary, yellow-red round mass with a size of ~6x5x5 mm in the adjacent part of the right upper eyelid and adjacent to the upper lacrimal point. (B) Intraoperative image: After the tumor was completely removed, the upper lacrimal point (shown by the arrow) was well preserved. (C) Gross specimen: Resected tumor specimens, ~5x5x5 mm in size. (D) Under squamous epithelium, dense proliferation of small spindle cells is seen; mitotic figures are clearly visible (arrows). (E) Scattered Dutton-like giant cells can be observed among the proliferating spindle cells (in circles). Immunohistochemical staining: The tumor cells were partially positive for (F) CD68, (G) CD163, (H) S-100, (I) CD1a and (J) CD10 and showed (K) diffuse strong positivity for cytoplasmic ALK. (L) Ki-67 proliferation index was ~10% (magnification, x200; scale bars, 100 μm). (M) Postoperative appearance: The surgical incision healed well without redness, swelling and recurrence. ALK, anaplastic lymphoma kinase.

China). Appropriate tissue controls for other markers were similarly sourced from the same institution. Negative controls were prepared by substituting the primary antibody with PBS. Immunohistochemical staining was evaluated independently by two pathologists. ALK positivity was defined as distinct cytoplasmic granular staining in >10% of tumor cells.

Table I. Main differential diagnoses of EFH.

Disease	Histomorphological features	Key immunophenotype	(Refs.)
EFH	Proliferation of epithelioid or spindle-like cells, occasionally with Touton-like giant cells	ALK(+), CD68(+/-), CD163(+/-), S-100(-/+)	(2)
Juvenile xanthogranuloma	Touton giant cells, foamy histiocytes	FXIIIa(+), CD14(+), ALK(-), CD1a(-)	(15)
Spitz nevus	Junctional or compound nevus, nests of epithelioid/spindle cells	S-100(+), SOX10(+), ALK(-), CD68(-)	(16)
Cutaneous myoepithelioma	Plasmacytoid or spindle cells, may show trabecular pattern	S-100(+), CK(+), p63(+), ALK(-), CD68(-)	(17)
Epithelioid sarcoma	Nodules of epithelioid cells, often with central necrosis	CK(+), EMA(+), loss of INI1 expression, ALK(-)	(18)
Granular cell tumor	Cells with abundant eosinophilic granular cytoplasm	S-100(+), CD68(+), ALK(-), inhibin(+)	(19)

EFH, epithelioid fibrous histiocytoma; ALK, anaplastic lymphoma kinase; CK, cytokeratin; EMA, epithelial membrane antigen.

Discussion

ALK-positive EFH is a rare cutaneous neoplasm that typically presents on the extremities of adults; its occurrence in the periocular region of children is exceptionally uncommon. To the best of our knowledge, only one case of ALK-positive EFH occurring in the eyelid of a child has been reported in the English-language literature prior to the present case described a 12-year-old female patient who presented with a nodule on the lower eyelid (9). Histopathological examination revealed an intradermal proliferation of epithelioid cells with abundant eosinophilic cytoplasm, and immunohistochemistry demonstrated positivity for CD68 and vimentin, with no mention of ALK testing, as ALK rearrangements in EFH had not yet been described at the time of that report. The tumor was treated by complete local excision with no recurrence documented during follow-up. In comparison, the present case occurred in a younger patient (7-year-old male) and involved the upper eyelid adjacent to the lacrimal punctum, a location that posed specific surgical considerations to preserve lacrimal function. Furthermore, the present case benefited from comprehensive immunohistochemical evaluation, including ALK testing, which confirmed the diagnosis with greater precision and highlighted the value of incorporating ALK immunohistochemistry in the workup of pediatric histiocytic-appearing eyelid tumors.

Histologically, EFH is characterized by epithelioid cells with abundant eosinophilic cytoplasm, vesicular nuclei and small nucleoli. The presence of Touton-like giant cells and low mitotic activity are also common features (10). Immunohistochemically, EFH typically shows variable expression of histiocytic markers, such as CD68 and CD163, which it is consistently ALK-positive due to underlying gene rearrangements (11). The characteristic molecular change of EFH is ALK gene rearrangement, which leads to the overexpression of ALK protein. ALK fusion partners reported in the current literature include VCL, dynactin 1, SP100 and cAMP-dependent protein kinase type II-α regulatory subunit (6). Different fusion partners can affect the subcellular localization and signal activation intensity of ALK protein. VCL-ALK fusion is mostly located under the plasma membrane, whilst SP100-ALK fusion is typically distributed in the nucleus (11,12). Identifying the type of ALK fusion has auxiliary value for the pathological diagnosis and differential diagnosis of EFH, where it can also provide the molecular basis for potential targeted intervention. In the present case, CD1a and CD10 showed partial immunoreactivity. CD1a is classically considered to be a marker of Langerhans cell histiocytosis. However, its expression can occasionally be detected in other histiocytic lesions, including indeterminate dendritic cell histiocytosis, certain subtypes of histiocytic sarcoma and reactive dendritic cell proliferative lesions (13), where its significance is not fully understood but may be associated with the presence of activated or immature dendritic cell populations. By contrast, CD10 is a membrane-associated peptidase expressed in a variety of mesenchymal cells and neoplasms, where its expression has also been reported in a subset of EFH. Positivity for these two aforementioned markers is not specific for EFH. However, when included in an immunohistochemical panel, they contribute to establishing a comprehensive staining profile and assist in excluding other entities in the differential diagnosis. Langerhans cell histiocytosis characteristically shows strong and diffuse expression of both CD1a and Langerin, which was not identified in the present case. In view of the notion that EFH is a benign tumor, local treatment is typically the main clinical treatment, where systemic targeted therapy is generally not required. Differential diagnosis should therefore be combined with morphology and immunophenotype. Juvenile xanthogranuloma (JXG) typically presents as Touton giant cells appearing morphologically, but it also expresses FXIIIa and CD14 whilst not expressing ALK. In addition, its Ki-67 proliferation index is low (<5%) (14,15). In the present case, Ki-67 was ~10%, which was higher compared with that of typical JXG, supporting EFH diagnosis. Spitz nevus is another similar condition that is common in children, but its cellular structure is typically distributed in nests, expressing S-100 and SOX10, whilst not expressing ALK and CD68 (16). By contrast, cutaneous myoepithelioma can express S-100 and cytokeratin, but rarely express CD68 and

ALK (17). Epithelioid sarcoma is a malignancy that frequently expresses CK and epithelial membrane antigen and is frequently accompanied by a lack of integrase interactor 1 expression (18). In granulosa cell tumor, S-100 and CD68 expression are typically positive, but the cytoplasm is characteristically granular and ALK expression is negative (19,20). The main histomorphological and immunophenotypic features distinguishing EFH from its key differential diagnoses are summarized in Table I.

To conclude, the present case illustrates an unusual presentation of ALK-positive EFH in the eyelid of a young male patient aged 7 years. Accurate diagnosis relied on a combination of clinical, histopathological and immunohistochemical findings. Complete surgical excision remained the treatment of choice, with favorable outcomes reported. Therefore, awareness of this entity is important for ophthalmologists and pathologists to ensure appropriate management and follow-up.

Acknowledgements

Not applicable.

Funding

The present report was supported by the scientific research project of Shandong School Health Association in 2025 (grant no. SDW2025067).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

ZS was the attending physician in charge of the case, responsible for diagnostic and therapeutic decisions and final review of the manuscript. ZZ and YuL contributed equally to collecting clinical data, literature review and writing the original draft. PS, WC and YaL were responsible for the analysis and interpretation of laboratory and pathological data and patient follow-up, respectively. ZS and YaL confirm the authenticity of all the raw data. JG provided essential clinical nursing information. All authors reviewed the manuscript and have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present case report was approved by the Ethics Committee of Jinan Mingshui Eye Hospital (approval no. 2025-016-01; Jinan, China).

Patient consent for publication

Written informed consent was obtained from the patient's legal guardian for the publication of the anonymized clinical information and pathological images.

Competing interests

The authors declare that they have no competing interests.

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