ALK-positive Histiocytosis of Umbilicus Subcutaneous with KIF5B-ALK Fusion: a Case Report

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Case Report

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Abstract

Background: Since the discovery of the first case of Anaplastic lymphoma kinase (ALK) -positive histiocytosis in 2008, originally described as a systemic, self-limiting disease in infants, the range of ALK-positive histiocytosis has recently been expanded to include localized diseases in older children and young adults.

Case presentation: We present the case of an 18-year-old female with periumbilical painless mass for 5 months, who underwent a resection of the mass. Pathological examination showed the tumor consists predominantly of fascicular to storiform growth of nonatypical spindle cells, admixed with lymphocytic infiltrates. The tumor spindle cells were diffusely positive for CD68, CD163 and ALK. Further, molecular tests revealed ALK gene fusion: Kinesin Family Member 5B (KIF5B) (E24)-ALK (E20), confirmed ALK-positive histiocytosis. The tumor has not recurred one and a half years after resection by follow-up examination.

Conclusion: ALK-positive histiocytosis in local lesion can achieve remission by complete resection and clinical follow-up showed a favorable prognosis.

Introduction

In 2008, Chan et al presented a series of three cases with a novel type of systemic histiocytosis termed “ALK-positive histiocytosis” (1). The disorder occurring in infants and young children typical features with hepatosplenomegaly and severe cytopenia. The tumor system affects the skin, spleen, liver, and bone marrow(2). On the contrary, ALK-positive histiocytosis occur in adults as localized lesions, such as breast, foot, nasal skin and cavernous sinus. Tumor cells have been found to be positive for histiocyte markers CD163, CD68, and CD4 (some cases show expression of S100 protein and factor XIIIa), but CD1a and langerin are always negative. There could also have Touton giant cells, and inflammatory infiltrates. Most patients have a favorable prognosis after treatment, and a few dead of ALK-positive histiocytosis(3). Usually, KIF5B was the main ALK gene fusion partner. In a few cases, ALK fusion involves other partners, including COLIA2, TRIM33 and TPM3 (4–6). Up to now, ALK-positive histiocytosis includes a wide spectrum of clinical manifestations in infants and adults, ranging from self-healing lesions to life-threatening systemic disease(7). However, the developmental origins of histiocytoses in patients are not well understood, and clinically meaningful therapeutic targets on targeted gene are undefined. Here we report a patient with localized ALK-positive histiocytosis and confer favorable response to resection.

Case Report

An 18-year-old female went to our hospital for periumbilical painless mass with 5 months. In the past five months. B-ultrasound showed that there was a hypoechoic mass(size: 11.7 mm × 8.2 mm ×11.8 mm) in the subcutaneous tissue of the umbilicus, with uneven internal echoes and clear boundaries (Fig. 1A). Then she accepted complete resection of the mass on June 16, 2019.

Microscopic examination showed predominantly of fascicular growth of nonatypical spindle cells, admixed with lymphocytic infiltrates and occasional lymphoid aggregates. Minor populations of plasma cells and eosinophils were also observed. The proliferated histiocytes were large cells with irregularly folded, deeply clefted or lobulated nuclei, fine chromatin and small nucleoli. Moreover, tumor spindle cells lacked nuclear atypia, and mitotic figures were extremely rare to absent (Fig. 2A). Immunohistochemistry (IHC) staining demonstrated strong positivity for CD68 and CD163, negative for CD207 (Langerin) and SMA (Fig. 2B-2E). The expression of Ki-67 has a labeling index of 2% (Fig. 2F). All immunohistochemistry results were listed in the Table 1. The IHC examination showed diffuse strong positive by two different ALK antibody clones, D5F3 and 1A4 (Fig. 2G-H). Break-apart fluorescence in situ hybridization (FISH) assays provided positive evidence of ALK gene rearrangements(Fig. 2I). In order to confirm the fusion site, a next-generation sequencing(NGS) was performed,which showed that the patient had ALK gene fusion: KIF5B (E24)-ALK (E20) (Fig. 3). The mass established the pathologic diagnosis of ALK-positive histiocytosis. The patient also underwent positron emission tomography (PET) after the local resection, indicating that the lesion was localized and had no systemic disorder (Fig. 1B). After one and a half years of follow-up, the patient had no recurrence of the disease and no systemic symptoms.

Table 1
Antibodies used for immunohistochemical staining and results

Antibody	Clone	Manufacturer	Result
CD68	PG-M1	DAKO	Positive
CD163	MRQ-26	DAKO	Positive
ALK	ALK1	DAKO	Positive
ALK	D5F3	ROCHE	Positive
B-RAF	VE1	ROCHE	Negative
CD1a	O10	DAKO	Negative
CD3	POLY	DAKO	Negative
CD20	L26	ROCHE	Negative
CD34	QBEnd10	GENE	Negative
Desmin	GTM2	MXB	Negative
EMA	E29	DAKO	Negative
Langerin	12D6	MXB	Negative
PCK	AE1/AE3	DAKO	Negative
S-100	POLY	DAKO	Negative
SMA	1A4	GENE	Negative

Discussion

ALK-positive histiocytosis are uncommon and often affect multiple organ systems, which pose diagnostic challenges for their rarity and the fact that the nosology of these lesions is being decide until now(4). The study of the clinicopathological features and prognosis of the disease is of great significance. Here, we reported a histiocytosis of umbilicus subcutaneous. Histomorphology showed fascicular to storiform growth of nonatypical spindle cells, admixed with lymphocytic infiltrates. The immunophenotyping and molecular findings confirmed a diagnosis of ALK-positive histiocytosis, which has described by Chang et al. in their recent series (3).

For the moment, the incidence of ALK-positive histiocytosis is relatively rare, and it needs to be differentiated from a variety of diseases. Immunohistochemistry showing negative CD207 (Langerin) can rule out Langerhans cell histiocytosis. Histiocytic cells become foamy and incorporated into Touton giant cells, which improved the differential diagnosis of juvenile xanthogranulom(JXG). JXG usually occurs in children with round or oval nuclei. Recently, few report presents ALK-positive in systemic JXG, rather than in localized lesions (8). Erdheim-Chester disease(ECD), a disease predominantly of adults with mean age of 55–60 years, but rare pediatric cases have been reported(9). Approximately 20% of patients with ECD have Langerhans cell histiocytosis lesions(10). Fibrosis in ECD is present in most cases and sometimes abandunt(11). Major showing BRAF-V600E mutation, ECD is a clonal systemic histiocytic proliferation most commonly involving bone, cardiovascular system and retroperitoneum(11). ALK-positive histiocytosis mainly occurs in young people without BRAF mutations. Epithelioid fibrous histiocytoma, often showing ALK expression, have to be distinguished from ALK-positive histiocytosis involving skin (12) (13). These cells, small or spindle shaped, have a more epithelioid form, lacking the expression of CD68 and S100(13). Differential diagnosis also including inflammatory myofibroblastoma (IMT), SMA are negative in atypical cells, and immunophenotype indicates histiocyte derived (14). Currently, ALK-positive histiocytosis has not specifically designated into the World Health Organization classification (15). Though Emile et al. in their classification included similar cases within the category of ECD, with the designation “extracutaneous or disseminated JXG with MAPK-activating mutation or ALK translocations”(12), current research suggest that ALK-positive histiocytosis differ from both ECD and JXG. The existing evidence supports that ALK-positive histiocytosis should have a separate classification, which is highly correlated with KIF5B-ALK fusion.

The literature review found that ALK-positive histiocytosis occurring in infants and young children typical features with hepatosplenomegaly and severe cytopenia (3). The tumor system affects the skin, spleen, liver, and bone marrow. On the contrary, histiocytosis occur in adults as localized lesions, such as breast, foot, nasal skin and cavernous sinus. Most infants can recover gradually or achieve complete remission with chemotherapy. All adults were completely relieved after surgical resection, and one unresectable case also achieved complete remission after crizotinib treatment. In our case, the localized ALK-positive histiocytosis harboring KIF5B-ALK has not recurred one and a half years until now, indicated a good prognosis.

In conclusion, ALK-positive histiocytosis should be distinguished from other tumors such as IMTs and spindled histiocytic reaction. The diagnosis can be critical for management, especially in systemic disorders and can be targeted using small molecule inhibitors. ALK expression or translocation testing was strongly recommend in every unusual histiocytic proliferative disorder to aid in identification of this entity. Though more localized ALK-positive histiocytosis cases showed favorable prognosis after completely resection, the long-term prognosis still needs follow-up.

Abbreviations

ALK: Anaplastic lymphoma kinase; KIF5B: Kinesin Family Member 5B; IHC: im- munohistochemistry; FISH: fluorescence in situ hybridization; NGS: Next-generation sequencing; PET:positron emission tomography; JXG: juvenile xanthogranulom; ECD: Erdheim-Chester disease; IMT: inflammatory myofibroblastoma; H&E: Hematoxylin and Eosin.

Declarations

Ethics approval and consent to participate

The present study was approved by the ethics committee of Tongji Medical College, Huazhong University of Science and Technology (reference no. S-377) and adhered to the tenets of the Declaration of Helsinki.

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials

All data generated or analyzed in the current article are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

YLZ ,JF and BH contributed equally as co-first authors in collecting clinical data and writing the paper. YW performed the immunohistochemistry and molecular staining experiments. HSS provided imaging and clinical information. XN and HXP designed the study. All authors read and approved the final manuscript.

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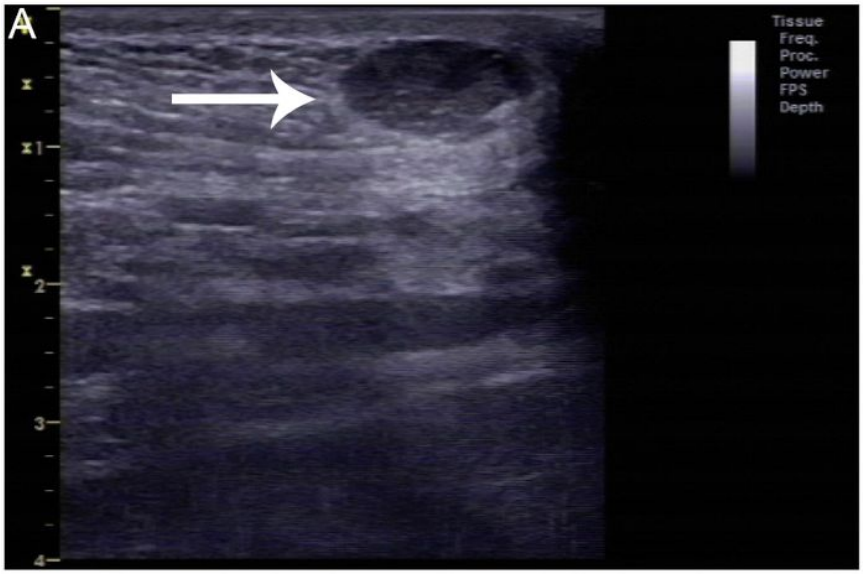
Figures



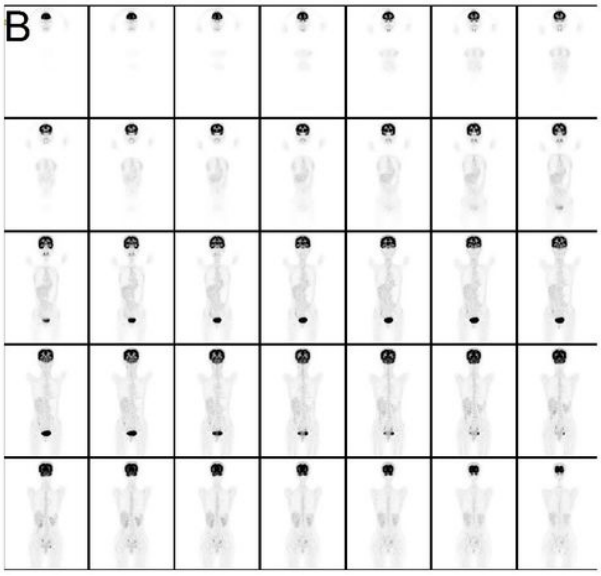


Figure 1

Imaging findings of ALK-positive histiocytosis. A. B-ultrasound showed a hypoechoic mass in the subcutaneous tissue above the umbilicus(size: 11.7 mm × 8.2 mm ×11.8 mm). B. PET-CT showed no sites of high metabolism throughout the body after lesion resection.

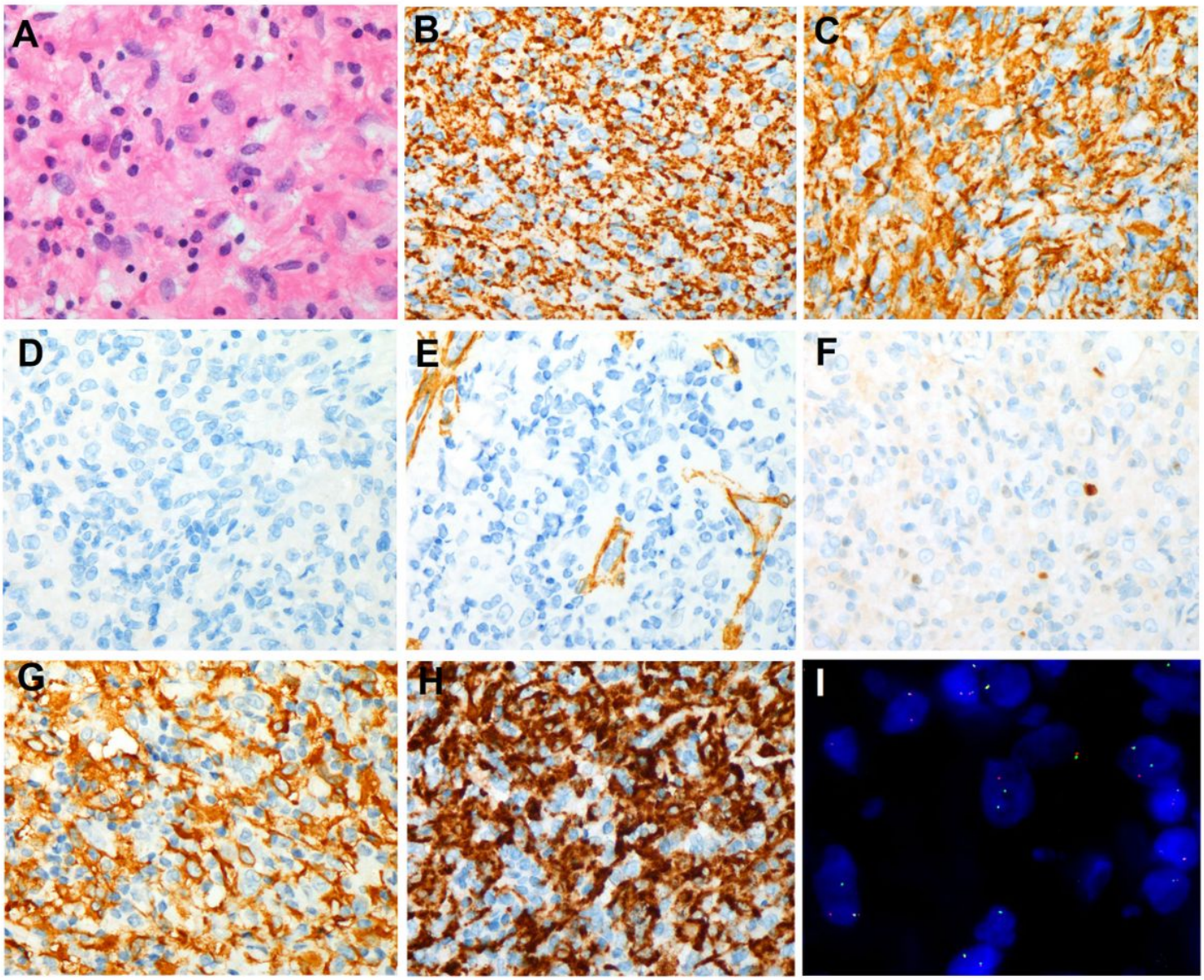


Figure 2

Histologic and molecular findings of ALK-positive histiocytosis of the umbilicus subcutaneous. A. Results of Hematoxylin and Eosin (H&E, magnification 400×) staining showed fascicular growth of nonatypical spindle cells, admixed with lymphocytic infiltrates. The proliferated histiocytes were large cells with irregularly folded, deeply clefted or lobulated nuclei, fine chromatin and small nucleoli. IHC staining indicated strong protein expression for CD68 (B) and CD168 (C), which are markers of histiocytic cells. IHC staining indicated negative expression for CD207 (D) and SMA (E). Ki-67 proliferation index was 2% by IHC staining (F). ALK 1A4 (G) and ALK D5F3 (H) immunoreactivity in histiocytic cells displayed a

diffuse cytoplasmic staining pattern (magnification ×400). I. Break-apart FISH assay shows that the tumor harbors gene rearrangements, positive result with the separation of the red and green signals(magnification ×1000).

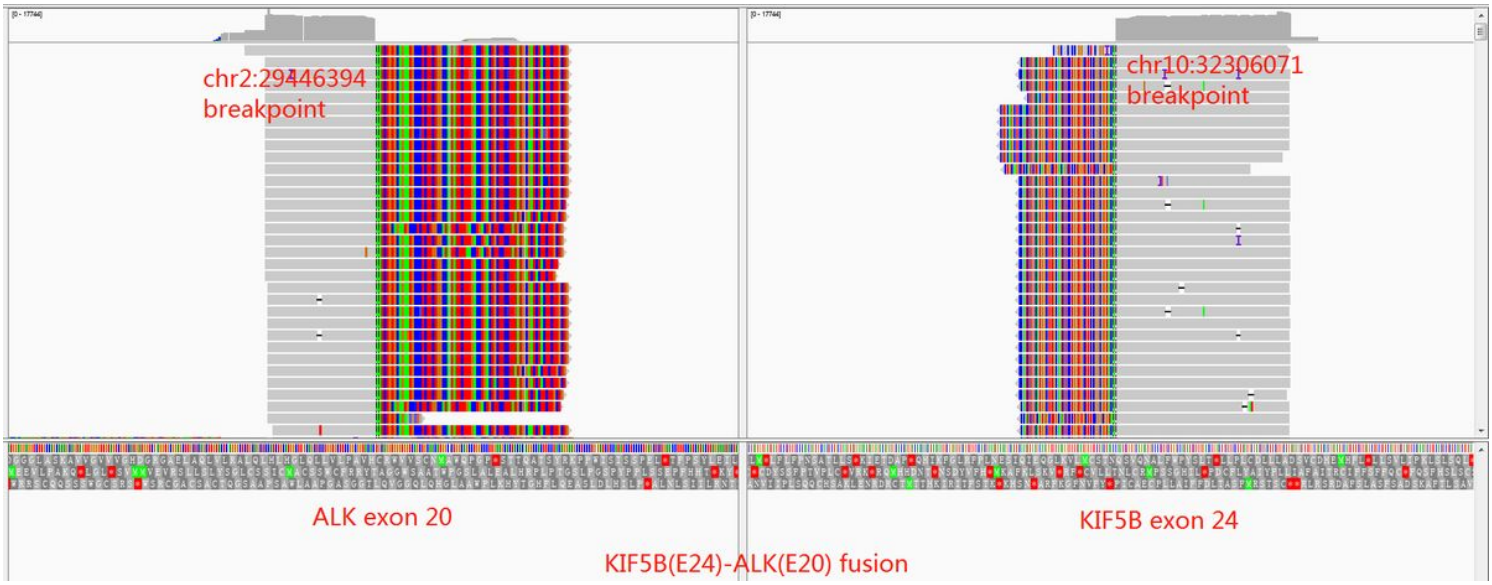


Figure 3

Result of NGS exhibiting the ALK (exon 20)-KIF5B (exon 24) fusion of ALK-positive histiocytosis. The break point of ALK gene 20 exon is chr2:29446394. The break point of KIF5B gene 24 exon is chr10:323066071.

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