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

Yili Zhu
Huazhong University of Science and Technology

Jun Fan
Wuhan Union Hospital

Bo Huang
Wuhan Union Hospital

Ying Wu
Huazhong University of Science and Technology

Heshui Shi
Wuhan Union Hospital

Xiu Nie (✉ niexiyishi@126.com)
Wuhan Union Hospital

Huaxiong Pan
Wuhan Union Hospital

Case Report

Keywords: Umbilicus subcutaneous, ALK-positive histiocytosis, KIF5B-ALK fusion

DOI: https://doi.org/10.21203/rs.3.rs-147658/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
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.

| 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 xanthogranuloma(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 abundant(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.

**Funding**

This work was supported by grants from the National Natural Science Foundation of China (No. 81773022 and 82072333); Natural Science Foundation of Hubei Province (No. 2020CFB808).

**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.

Acknowledgements

The authors thank our patient and her family, as well as our colleagues at Wuhan union hospital. Consent for publication has been obtained from the patient herself.

References

1. Chan JK, Lamant L, Algar E, Delsol G, Tsang WY, Lee KC, et al. ALK+ histiocytosis: a novel type of systemic histiocytic proliferative disorder of early infancy. Blood. 2008 Oct 1;112(7):2965-8. PubMed PMID: 18660380. Epub 2008/07/29. eng.

2. Huang H, Gheorghe G, North PE, Suchi M. Expanding the Phenotype of ALK-positive Histiocytosis: A Report of 2 Cases. Pediatric and developmental pathology : the official journal of the Society for Pediatric Pathology and the Paediatric Pathology Society. 2018 Sep-Oct;21(5):449-55. PubMed PMID: 29224419. Epub 2017/12/12. eng.

3. Chang KTE, Tay AZE, Kuick CH, Chen H, Algar E, Taubenheim N, et al. ALK-positive histiocytosis: an expanded clinicopathologic spectrum and frequent presence of KIF5B-ALK fusion. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2019 May;32(5):598-608. PubMed PMID: 30573850.

4. Lucas CG, Gilani A, Solomon DA, Liang X, Maher OM, Chamyan G, et al. ALK-positive histiocytosis with KIF5B-ALK fusion in the central nervous system. Acta Neuropathol. 2019 Aug;138(2):335-7. PubMed PMID: 31119374. Pubmed Central PMCID: PMC6712982. Epub 2019/05/24. eng.

5. Tran TAN, Chang KTE, Kuick CH, Goh JY, Chang CC. Local ALK-Positive Histiocytosis With Unusual Morphology and Novel TRIM33-ALK Gene Fusion. International journal of surgical pathology. 2020 Nov 27:1066896920976862. PubMed PMID: 33243034.

6. Kashima J, Yoshida M, Jimbo K, Izutsu K, Ushiku T, Yonemori K, et al. ALK-positive Histiocytosis of the Breast: A Clinicopathologic Study Highlighting Spindle Cell Histology. The American journal of surgical pathology. 2020 Aug 20. PubMed PMID: 32826530.

7. Emile JF, Abla O, Fraitag S, Horne A, Haroche J, Donadieu J, et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood. 2016 Jun 2;127(22):2672-81. PubMed PMID: 26966089. Pubmed Central PMCID: 5161007.

8. Xu J, Huang X, Wen Y, Pan Z, Lian H, Zhao M, et al. Systemic Juvenile Xanthogranuloma has a Higher Frequency of ALK Translocations than BRAFV600E Mutations. J Am Acad Dermatol. 2020 Aug 18. PubMed PMID: 32822792. Epub 2020/08/22. eng.
9. Globerman H, Burstein S, Girardina PJ, Winchester P, Frankel S. A xanthogranulomatous histiocytosis in a child presenting with short stature. Am J Pediatr Hematol Oncol. 1991 Spring;13(1):42-6. PubMed PMID: 1903027. Epub 1991/01/01. eng.

10. Hervier B, Haroche J, Arnaud L, Charlotte F, Donadieu J, Neel A, et al. Association of both Langerhans cell histiocytosis and Erdheim-Chester disease linked to the BRAFV600E mutation. Blood. 2014 Aug 14;124(7):1119-26. PubMed PMID: 24894769.

11. Emile JF, Abla O, Fraitag S, Horne A, Haroche J, Donadieu J, et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood. 2016 Jun 2;127(22):2672-81. PubMed PMID: 26966089. Pubmed Central PMCID: PMC5161007. Epub 2016/03/12. eng.

12. Dickson BC, Swanson D, Charames GS, Fletcher CD, Hornick JL. Epithelioid fibrous histiocytoma: molecular characterization of ALK fusion partners in 23 cases. Mod Pathol. 2018 May;31(5):753-62. PubMed PMID: 29327718. Epub 2018/01/13. eng.

13. Kazakov DV, Kyrpychova L, Martinek P, Grossmann P, Steiner P, Vanecek T, et al. ALK Gene Fusions in Epithelioid Fibrous Histiocytoma: A Study of 14 Cases, With New Histopathological Findings. Am J Dermatopathol. 2018 Nov;40(11):805-14. PubMed PMID: 29329131. Epub 2018/01/13. eng.

14. Gupta GK, Xi L, Pack SD, Jones JB, Pittaluga S, Raffeld M, et al. ALK-positive histiocytosis with KIF5B-ALK fusion in an adult female. Haematologica. 2019 Nov;104(11):e534-e6. PubMed PMID: 31371408. Pubmed Central PMCID: PMC6821621. Epub 2019/08/03. eng.

15. Rodig SJ, Mino-Kenudson M, Dacic S, Yeap BY, Shaw A, Barletta JA, et al. Unique clinicopathologic features characterize ALK-rearranged lung adenocarcinoma in the western population. Clin Cancer Res. 2009 Aug 15;15(16):5216-23. PubMed PMID: 19671850. Pubmed Central PMCID: PMC2865649. Epub 2009/08/13. eng.

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.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CAREchecklistEnglish2013.pdf