MHICC

6/25/2025

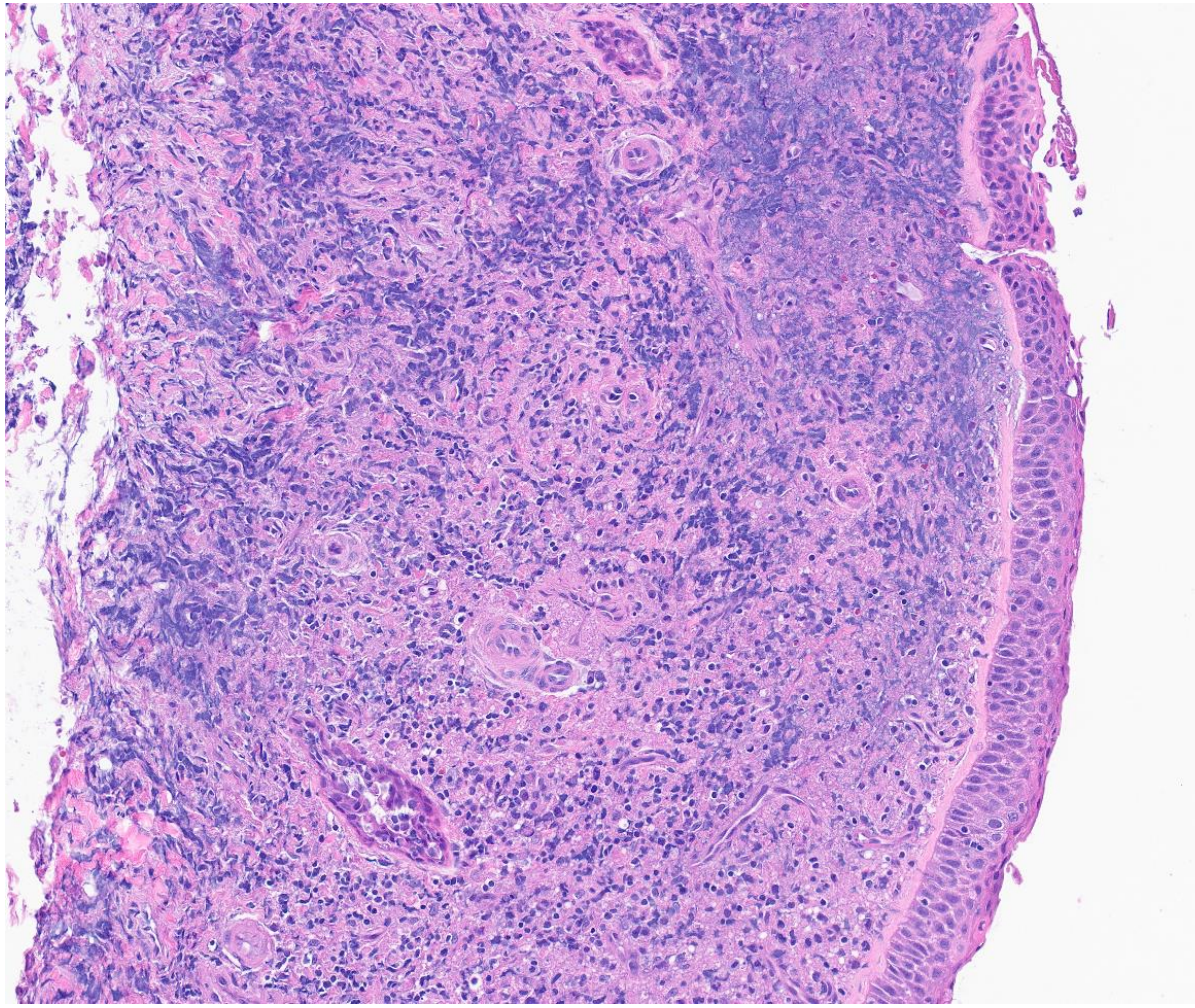
Case 1

Clinical Information

- 3 (nearly 4)-year old boy, no significant past medical history, presented with stridor.
- Direct laryngoscopy revealed a ~0.5 cm subglottic mass arising from the right cricoid.
- CT scan revealed no significant lymphadenopathy.
- CBC and LDH were within normal limits for age.
- A biopsy of the subglottic mass was performed. Concern for malignancy, but a hematolymphoid neoplasm was not specifically suspected.

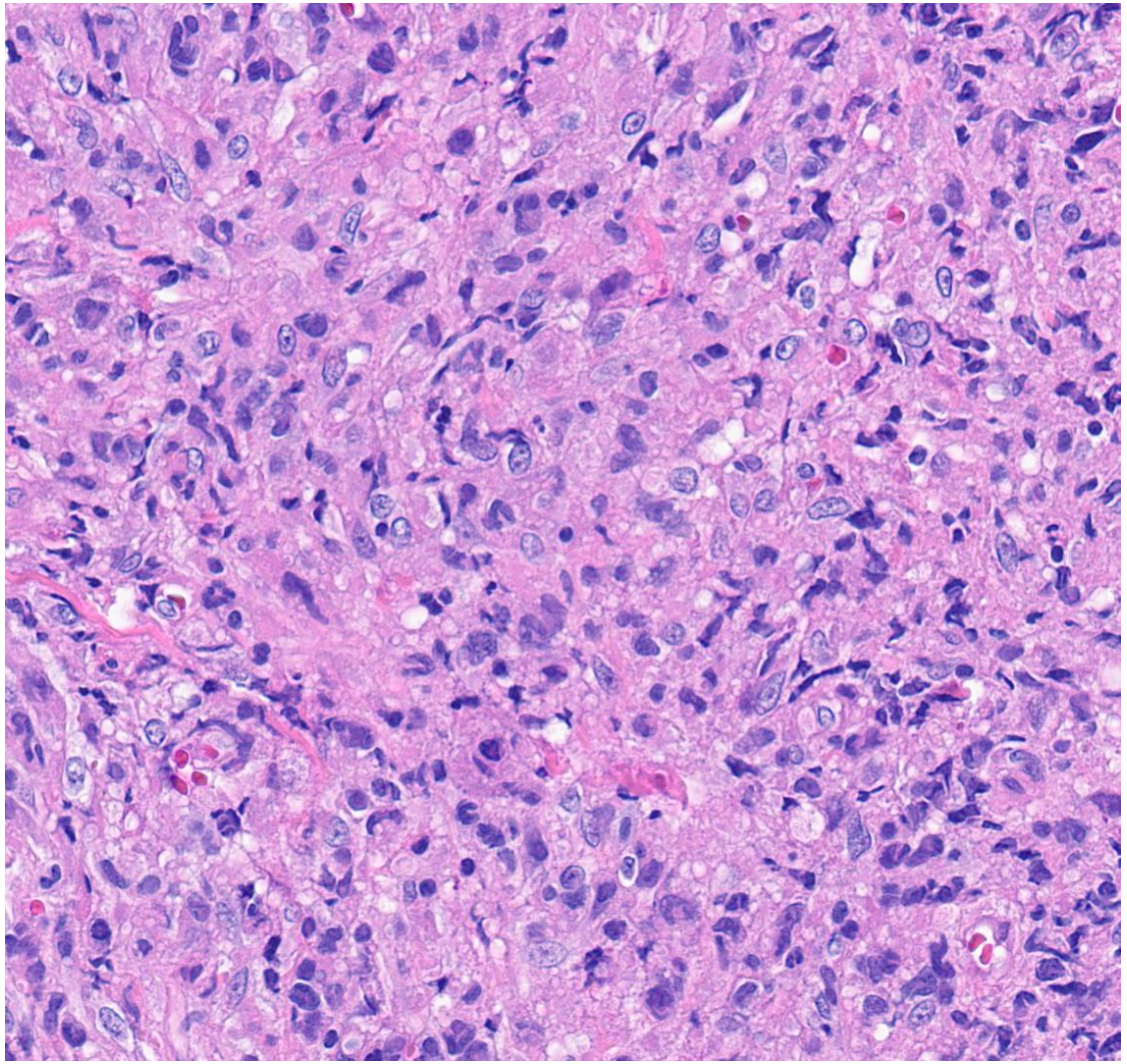
Details of Microscopic Findings

- Biopsy was received in formalin. No separate tissue sent for flow cytometry or karyotype.
- Tissue showed stratified squamous-lined mucosa with a dense infiltrate of cells in the mucosa.
- Cells are randomly distributed.
  - No glands, no rosetting.
  - No obvious fascicles, bundles, storiform pattern, etc.



Details of Microscopic Findings

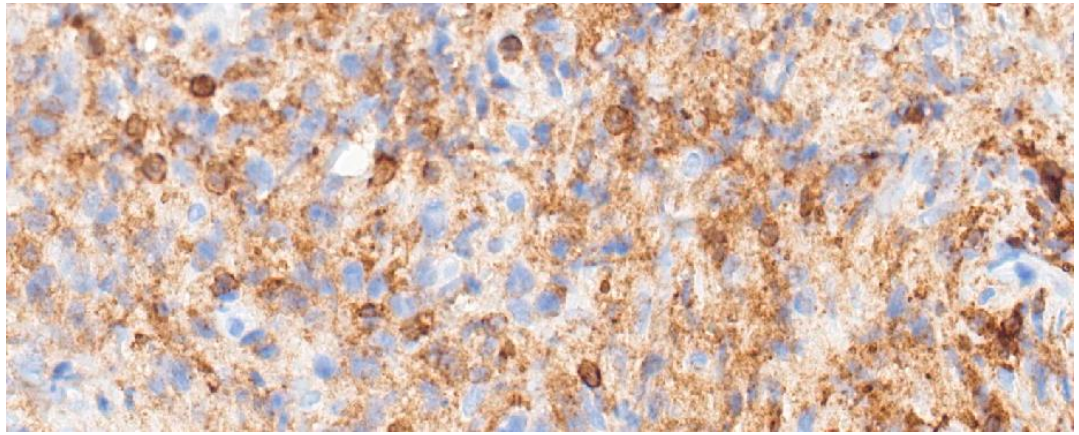
- Cells are medium to large-size with irregular, but not high-grade, nuclei.
- Nucleoli are visible but not very large.
- Cytoplasm is abundant, pink, syncytial.



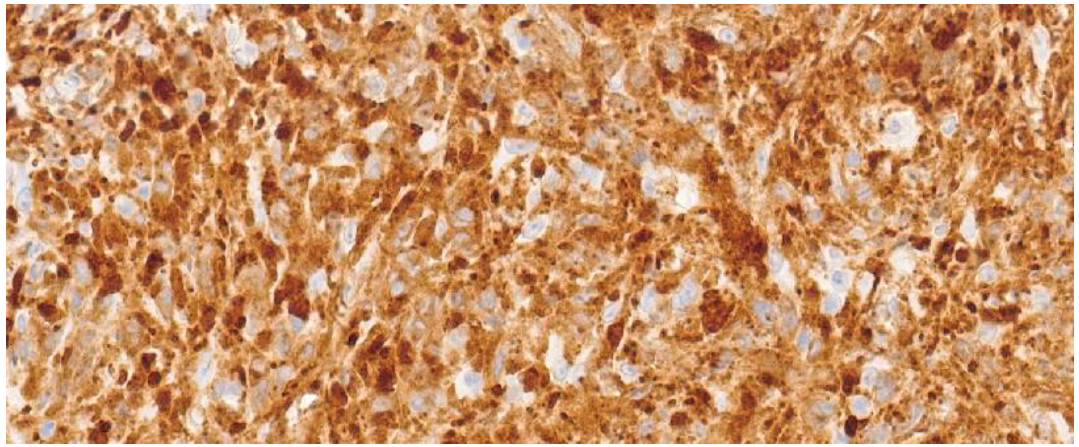
Immunophenoytpe

CD45	Positive
ALK-1 (D5F3 clone)	Positive
CD163	Positive
Fascin	Positive
CD1a	Negative
Muscle markers: • MyoD1 • Desmin • SMA • Myogenin • MSA	Negative
T-cell markers (CD3, CD2, CD5, CD7)	Negative
B cell and plasmablastic markers (CD20, CD138, MUM1, BLIMP1, OCT-2)	Negative
EBV in-situ hybridization	Negative
Cytokeratin (AE1/AE3)	Negative
S100	Negative
CD34	Focal positive
INI-1	Retained

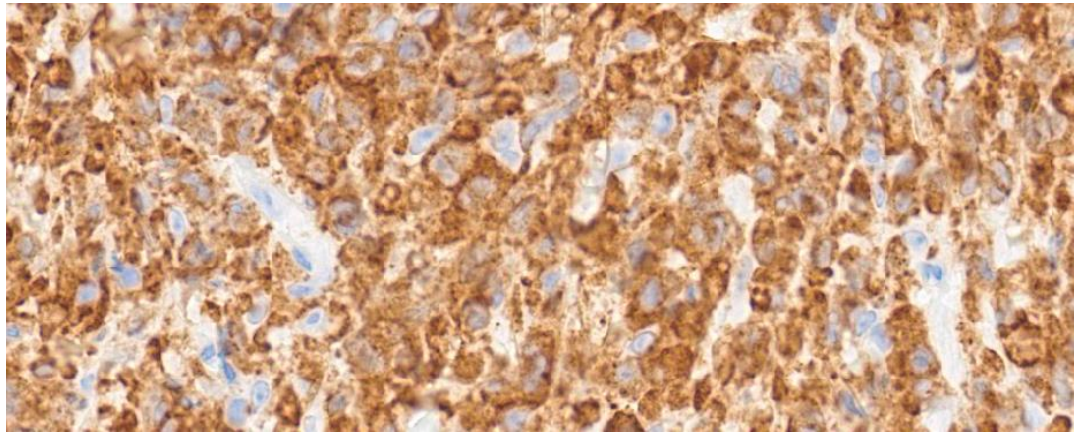
CD45



ALK-1



CD163



Molecular Studies

FoundationHeme

Confirms *KIF5B*::*ALK* fusion

Sample qualified for low tumor purity. Sensitivity for detecting copy-number alterations (including in *ERBB2*) and other genomic alterations may be reduced. Refer to the appendix for limitations statements.

This report, or some of the results within, is qualified due to sample insufficiency or sample quality. Please contact FMI Client Services for more information and, if within 30 days of the report date, to discuss potential options for retesting the patient at no charge.

Biomarker Findings

Microsatellite status - Cannot Be Determined [α]

Tumor Mutational Burden - Cannot Be Determined

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

ALK **KIF5B-ALK fusion**

α Patients with Microsatellite status of Cannot Be Determined should be re-tested with an orthogonal (alternative) method.

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***ALK*** **KIF5B-ALK fusion** (p. 5)
- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Alectinib** (p. 6), **Brigatinib** (p. 6), **Ceritinib** (p. 6), **Crizotinib** (p. 7), **Entrectinib** (p. 7), **Lorlatinib** (p. 8)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 9)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - Cannot Be Determined	**No therapies or clinical trials.** See Biomarker Findings section
Tumor Mutational Burden - Cannot Be Determined	**No therapies or clinical trials.** See Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
ALK - KIF5B-ALK fusion	none	Alectinib
		Brigatinib
		Ceritinib
		Crizotinib
		Entrectinib
		Lorlatinib

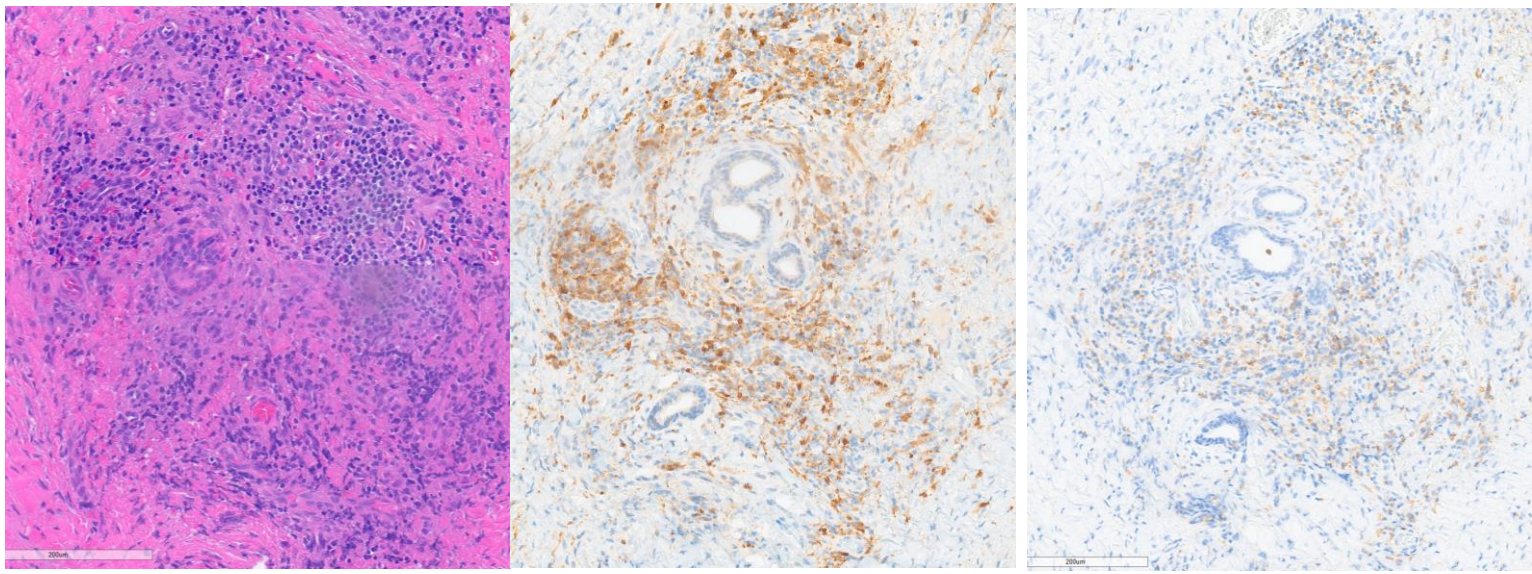
3 Trials see p. 9

Diagnosis

ALK-positive histiocytosis

Case Follow up

2-month follow-up biopsy



H&E ALK CD68 –KP1

- The patient underwent 2 additional surgical procedures (2 and 3 months after initial diagnosis), both with biopsies showing residual disease.
- Direct visualization (~6 months after diagnosis, 3 months after last biopsy) showed well-healed resection site without recurrence.
- Plan to defer any systemic therapy, re-evaluate in 6 months.

Features of diagnosis

- Recognized by WHO V and ICC.
- Requirements (WHO V):
  - Histiocytic lesion with at least two of the following positive: CD163, CD68, CD14, CD4, lysozyme.
  - Lack of high-grade atypia (i.e., not histiocytic sarcoma).
  - ALK-positive by IHC, ideally with demonstration of *ALK* translocation.
- Notably positive for S100 in 50% of cases, but negative for CD1a, langerin.
- Negative for CD30.

History of diagnosis

- First reported in 2008 (3 cases), all infants, involving liver.[1]
  - All three patients survived after years of follow-up, including one who received no cytotoxic therapy.
  - All ALK-positive by IHC, with 1/3 showing an *ALK*::*TMP3*.
    - Partner not identified in other two cases.
- 2019, a new paper (many of the same authors) described an expanded clinicopathologic spectrum.[2]
  - Still mostly infants but included older children and one adult.
  - Most common fusion: *KIF5B*::*ALK.*
  - Overall, good outcomes, but some poorer outcomes.

1. Chan JK, Lamant L, Algar E, Delsol G, Tsang WY, Lee KC, Tiedemann K, Chow CW. ALK+ histiocytosis: a novel type of systemic histiocytic proliferative disorder of early infancy. Blood. 2008 Oct 1;112(7):2965-8. doi: 10.1182/blood-2008-03-147017. Epub 2008 Jul 25. PMID: 18660380.
2. Chang KTE, Tay AZE, Kuick CH, Chen H, Algar E, Taubenheim N, Campbell J, Mechinaud F, Campbell M, Super L, Chantranuwat C, Yuen ST, Chan JKC, Chow CW. ALK-positive histiocytosis: an expanded clinicopathologic spectrum and frequent presence of KIF5B-ALK fusion. Mod Pathol. 2019 May;32(5):598-608. doi: 10.1038/s41379-018-0168-6. Epub 2018 Dec 20. PMID: 30573850.

History of diagnosis

Sex	Age	Ethnicity	Extent	Fusion	Treatment	Follow-up
F	Neonate	Caucasian	SLB, skin	*TPM3*	Chemo	NED
F	2 months	Thai	SLB	*KIF5B*	Chemo	NED
F	3 months	Chinese	SLB	Failure	Chemo	NED
F	3 months	Chinese	SLB	Failure	Abx	NED
M	3 months	Caucasian	LB, skin, kidney, lung	*KIF5B*	Chemo	Skin nodules, otherwise NED
M	2 years, 3 months	Caucasian	Nasal skin papule	*KIF5B*	Excision (inc.)	NED
M	2 years, 9 months	Middle Eastern	B, intestine, CNS	Unknown*	Chemo	Died @ 2 mo.
M	15 years	Caucasian	Cavernous sinus	*KIF5B*	Crizotinib	NED
M	16 years	Chinese	Foot skin and soft tissue	*COLIA2*	Resection (?)	NED
F	40 years	Chinese	Breast	*KIF5B*	Excision (comp.)	NED

Adapted from: Chang KTE, Tay AZE, Kuick CH, Chen H, Algar E, Taubenheim N, Campbell J, Mechinaud F, Campbell M, Super L, Chantranuwat C, Yuen ST, Chan JKC, Chow CW. ALK-positive histiocytosis: an expanded clinicopathologic spectrum and frequent presence of KIF5B-ALK fusion. Mod Pathol. 2019 May;32(5):598-608. doi: 10.1038/s41379-018-0168-6. Epub 2018 Dec 20. PMID: 30573850.

S: Spleen; L: Liver; B: Bone marrow
*Only breakapart FISH was performed

History of diagnosis

Sex	Age
F	Neonate
F	2 months
F	3 months
F	3 months
M	3 months
M	2 years, 3 months
M	2 years, 9 months
M	15 years
M	16 years
F	40 years

- Mostly <1 year.
- Mostly female in youngest cohort, mostly male >1 year.
- Rare in adults.

Adapted from: Chang KTE, Tay AZE, Kuick CH, Chen H, Algar E, Taubenheim N, Campbell J, Mechinaud F, Campbell M, Super L, Chantranuwat C, Yuen ST, Chan JKC, Chow CW. ALK-positive histiocytosis: an expanded clinicopathologic spectrum and frequent presence of KIF5B-ALK fusion. Mod Pathol. 2019 May;32(5):598-608. doi: 10.1038/s41379-018-0168-6. Epub 2018 Dec 20. PMID: 30573850.

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History of diagnosis

Sex	Age	Ethnicity	Extent
F	Neonate	Caucasian	SLB, skin
F	2 months	Thai	SLB
F	3 months	Chinese	SLB
F	3 months	Chinese	SLB
M	3 months	Caucasian	LB, skin, kidney, lung
M	2 years, 3 months	Caucasian	Nasal skin papule
M	2 years, 9 months	Middle Eastern	B, intestine, CNS
M	15 years	Caucasian	Cavernous sinus
M	16 years	Chinese	Foot skin and soft tissue
F	40 years	Chinese	Breast

- More likely systemic in younger age groups; more likely localized in older.

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S: Spleen; L: Liver; B: Bone marrow
*Only breakapart FISH was performed

History of diagnosis

- Most patients do very well, including some treated with surgery only (even with positive margins).
- Single fatality was in only non-infant systemic case.
- *KIF5B* was overwhelmingly most common fusion partner.
- Note that cavernous sinus case was inoperable, hence crizotinib treatment.

Extent	Fusion	Treatment	Follow-up
SLB, skin	*TPM3*	Chemo	NED
SLB	*KIF5B*	Chemo	NED
SLB	Failure	Chemo	NED
SLB	Failure	Abx	NED
LB, skin, kidney, lung	*KIF5B*	Chemo	Skin nodules, otherwise NED
Nasal skin papule	*KIF5B*	Excision (inc.)	NED
B, intestine, CNS	Unknown*	Chemo	Died @ 2 mo.
Cavernous sinus	*KIF5B*	Crizotinib	NED
Foot skin and soft tissue	*COLIA2*	Resection (?)	NED
Breast	*KIF5B*	Excision (comp.)	NED

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S: Spleen; L: Liver; B: Bone marrow
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History of diagnosis

- Immunophenotype:
  - Positive for CD68, CD163.
  - 4/8 tested cases positive for S100, but CD1a and langerin negative.
  - BRAF V600E stain negative in all cases (molecular testing not reported).
- Conclusions of paper:
  - Clinicopathologic spectrum is wider than thought in 2008.
  - Even with initial worrisome picture (systemic disease), there is often spontaneous resolution with supportive care, though surgery and/or systemic therapy may also be appropriate.

Differential diagnosis

- *ALK*-translocated neoplasms:
  - ALCL (usual partner is *NPM;* usually positive for at least some T cell markers).
  - ALK-positive LBL (usual partner is *CLTC*; positive for at least some B cell or plasmablastic markers).
  - Non-hematopoietic:
    - Inflammatory myofibroblastic tumor (many partners).
    - Epithelioid inflammatory myofibroblastic sarcoma (*RANBP2)*.
    - Epithelioid fibrous histiocytoma (*SQSTM1*, *VCL*).
      - Previously a variant of dermatofibroma.
    - Various carcinomas, e.g. lung.

Differential diagnosis

- Histiocytic / ALK-negative neoplasms:

Diagnosis	BRAFV600E	S100	CD1a	Langerin	ALK	Notes
ALK+ histiocytosis	-	+ (50%)	-	-	+	
Rosai-Dorfman	Rare	+	-	-	-§	Emperipolesis; LN involvement.
Erdheim-Chester	+ (50-60%)	- (usually)	-	-	-	Systemic but spares, L, S. Adults.
Langerhaans CH/S	Common	+	+	+	-	
Indeterminate DCT	Rare	+	+	-	-	Usually (not always) in skin.
Interdigitating DCS	Some	+	-	-	-	Rare, usually adults.
Histiocytic sarcoma	Some	Variable	-	-	-§	Nuclear pleomorphism
Juvenile xanthogranuloma	Unclear†	Minority (patchy)	-	-	-‡	Usually (not always) in skin.

*LCH cases usually (80%) have some *MAPK* pathway gene mutation; BRAFV600e is most common and easily assessed by IHC, but others, especially *MAP2K1* mutation, may be present instead. *MAPK* pathway mutation can be suggested by cyclin D1 expression or p-ERK expression. Molecular characterization of LCH is more extensive than of LCS, which only shows *MAPK* pathway mutation in a subset of cases.

†Molecular data for JXG are not extensive. Most common mutations are in *MAPK* pathway. However, although *BRAF*V600E mutation has been described in some JXG cases, WHO recommends reconsidering whether some apparent JXG cases with *BRAF*V600E mutation could actually be Erdheim-Chester disease.

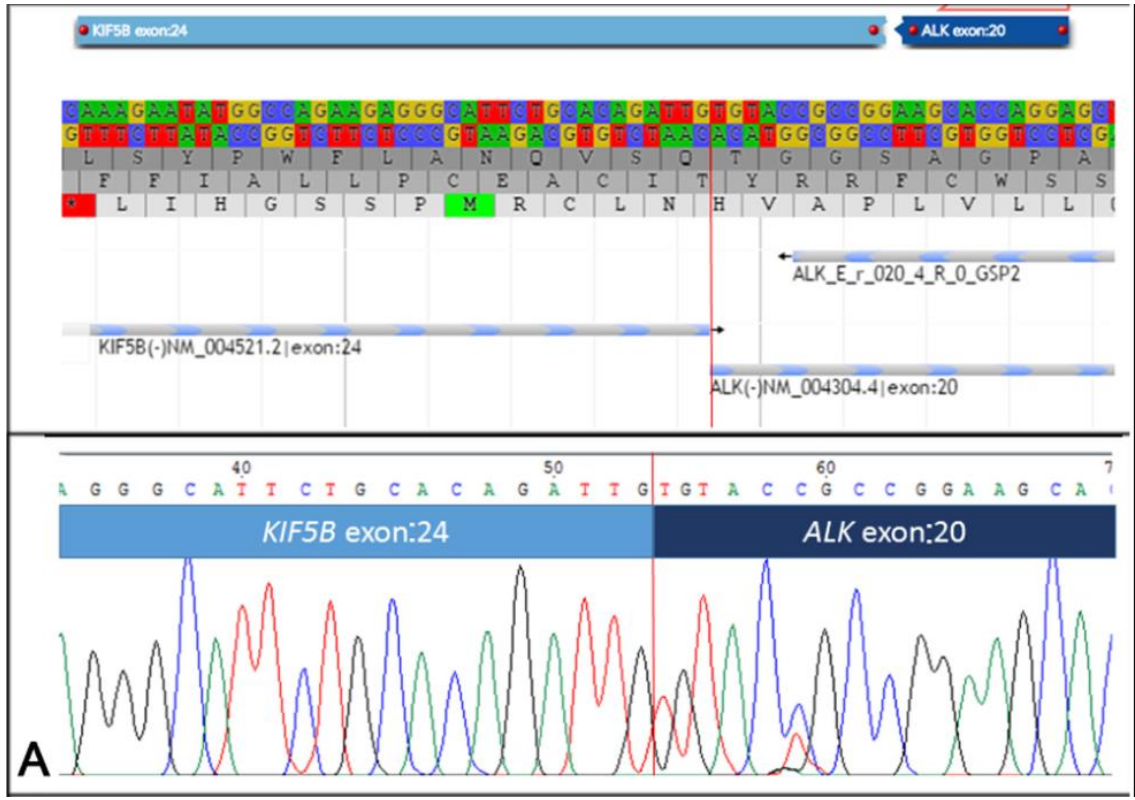
‡By definition, per WHO V

§ Described as negative by WHO V, but not absolute criterion.

What is *KIF5B?*

- Encodes a ubiquitous motor protein involved in intracellular transport.
- Fusion with *ALK* results in ubiquitously-expressed RTK.
  - Detected in 5/10 cases, and 5/7 cases in which a partner was actually identified.
- 2016 paper[3] searching for targetable kinase fusions identified 2 (of 24) cases of histiocytic neoplasms (diagnosed as EC) with *ALK*::*KIF5B.*
  - 25 yo, skin; 50 yo, liver.
  - Both were *BRAF*V600E-negative.
- Also identified in lung carcinoma, but with a different breakpoint (18 or 20).

Chang KTE, Tay AZE, Kuick CH, Chen H, Algar E, Taubenheim N, Campbell J, Mechinaud F, Campbell M, Super L, Chantranuwat C, Yuen ST, Chan JKC, Chow CW. ALK-positive histiocytosis: an expanded clinicopathologic spectrum and frequent presence of KIF5B-ALK fusion. Mod Pathol. 2019 May;32(5):598-608. doi: 10.1038/s41379-018-0168-6. Epub 2018 Dec 20. PMID: 30573850.



3. Diamond EL, Durham BH, Haroche J, Yao Z, Ma J, Parikh SA, Wang Z, Choi J, Kim E, Cohen-Aubart F, Lee SC, Gao Y, Micol JB, Campbell P, Walsh MP, Sylvester B, Dolgalev I, Aminova O, Heguy A, Zappile P, Nakitandwe J, Ganzel C, Dalton JD, Ellison DW, Estrada-Veras J, Lacouture M, Gahl WA, Stephens PJ, Miller VA, Ross JS, Ali SM, Briggs SR, Fasan O, Block J, Héritier S, Donadieu J, Solit DB, Hyman DM, Baselga J, Janku F, Taylor BS, Park CY, Amoura Z, Dogan A, Emile JF, Rosen N, Gruber TA, Abdel-Wahab O. Diverse and Targetable Kinase Alterations Drive Histiocytic Neoplasms. Cancer Discov. 2016 Feb;6(2):154-65. doi: 10.1158/2159-8290.CD-15-0913. Epub 2015 Nov 13. PMID: 26566875;

Conclusions

- ALK-positive histiocytosis is a distinct diagnosis.
  - Pediatric predilection; broad clinicopathologic spectrum.
  - May have severe presentation, but usually good outcome:
    - Spontaneous resolution.
    - Surgery.
    - Chemotherapy.
    - ALK-inhibitors.
  - Among histiocytic neoplasms, ALK positivity by IHC is fairly specific.
    - Unclear whether *BRAF*V600E-negative Erdheim-Chester can have *ALK* translocation.
  - Among tumors overall, *KIF5B* partner is nearly 100% specific (but not 100% sensitive) for this diagnosis.