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European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

14/10/2026



Presenter: Dr. Bianca Macri

Expert: MD, PhD Milen Minkov

A challenging ALCL diagnosis complicated by secondary HLH

Moderation:
Martin Schalling

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COI declaration

I have no COI to declare

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Clinical presentation

5 year-old girl

- Persistent fever
- Cervical lymphadenopathy
- Axillary lymphadenopathy
- Skin lesion on the back



Positive serology for *Bartonella Henselae*



Suspicion of cat-scratch disease



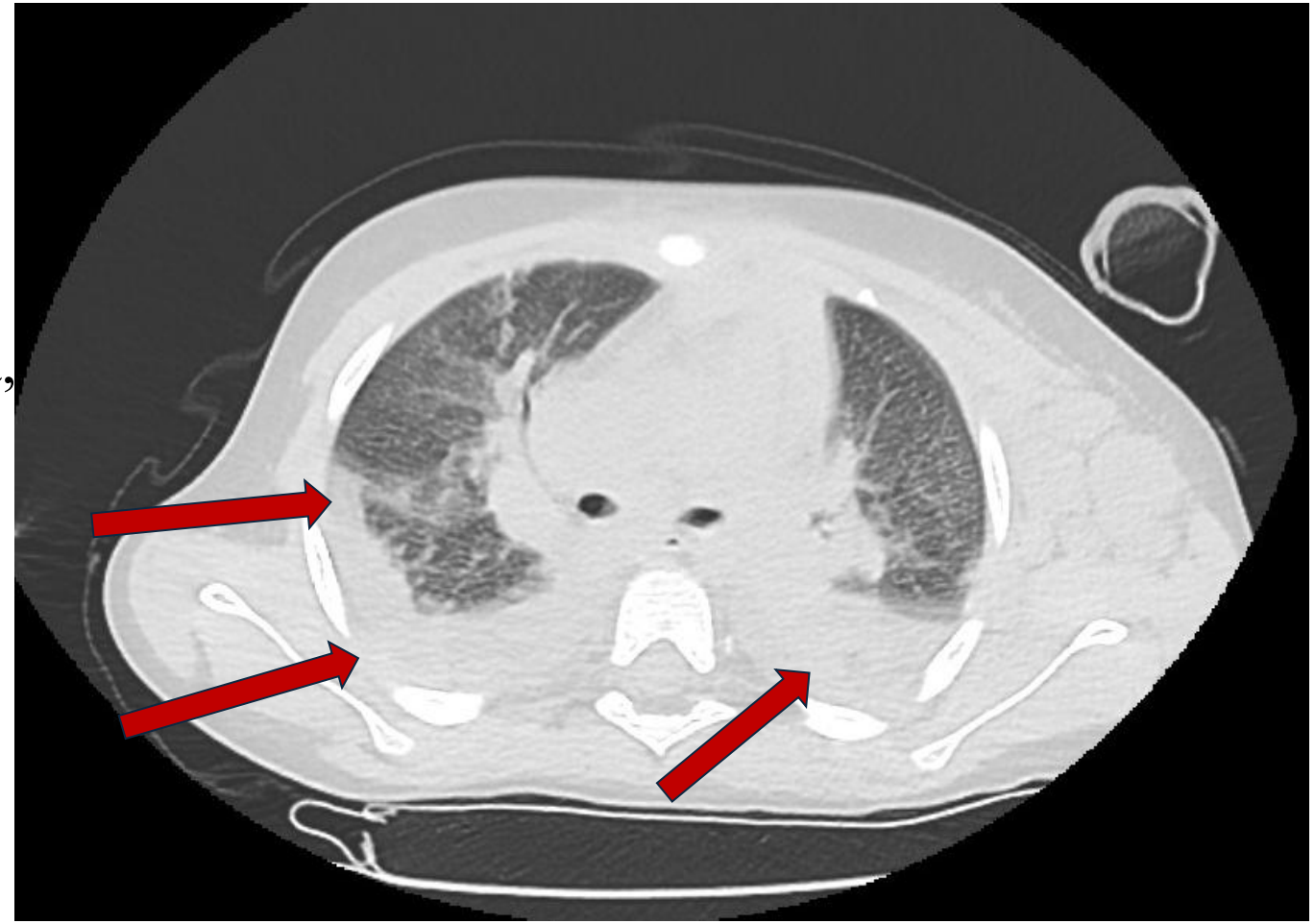
Start of antibiotic treatment

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Despite ongoing treatment…

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- Persistent fever
- Persistent lymphadenopathy
- Clinical worsening (polypnea, low SpO2, swelling)



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Question 1

What is your primary suspicion?

1. Bartonella-related pneumonia

2. Hyperinflammatory syndrome at onset

3. Other bacterial pneumonia (ex: tuberculosis)

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Hyperinflammatory syndrome onset

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	15.03.25	17.03.25
Ferritin	2178	3823
triglycerides (mg/dl)	287	438
Fibrinogen (mg/dl)	89	85
Hb (g/dl)	8.7	10.3
PLT (mmc)	68000	24000

- lymph-node excision biopsy was performed

Table 1. Diagnostic criteria.

HLH-2004 diagnostic criteria	
Feature	Cut off
1. Fever	
2. Splenomegaly	
3. Cytopenia	≥2 cell lines
Hemoglobin	< 90 g/L (neonates <100 g/L)
Platelets	<100x10⁹/L
Neutrophils	<1x10⁹/L
4. Hyperferritinemia	>500 µg/L
5. Hypofibrinogenemia	< 1.5 g/L
or hypertriglyceridemia	> 3 mmol/L
6. Elevated soluble CD25	> 2400 U/mL
7. Hemophagocytosis	Bone marrow, other tissues
8. Reduced or absent NK cytotoxicity	
Other features	
Elevated transaminases and bilirubin	
Elevated lactate dehydrogenase	
Elevated d-dimers	
Elevated cerebrospinal fuid cells and/or protein	

NK: natural killer cells.

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Other relevant data

	12.03.25	15.03.25	17.03.25
EBV-DNA (UI/ml)	324	2861	296

Bone marrow and PB samples were sent to look for t 2;5 and tested positive

Malignancy-associated haemophagocytic lymphohistiocytosis

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Question 2

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How should HLH be optimally managed in this progressively worsening scenario?

1. Start steroids and Intravenous immunoglobulins

2. Start chemotherapy

3. Give antibiotics

4. Do further diagnostic evaluations (e.g., flow cytometric degranulation test, perforin)

5. Start steroids, intravenous immunoglobulins and chemotherapy + do more testing

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How we treated our patient

- Start Dexamethasone 10 mg/m2
- IgEV
- Anakinra

- Supportive therapy
- HFNC
- NIV (transfer to the PICU)

- Start lymphoma treatment!!

EXPERIMENTAL AND THERAPEUTIC MEDICINE 26: 423, 2023

Secondary hemophagocytic lymphohistiocytosis in children (Review)

CHIARA BENEVENUTA, ILARIA MUSSINATTO, CECILIA ORSI and FABIO S. TIMEUS

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DOI: 10.3892/etm.2023.12122

children

MDPI

Article

Hemophagocytic Lymphohistiocytosis as Initial Presentation of Malignancy in Pediatric Patients: Rare but Not to Be Ignored

Hye-ji Han [1], Kyung Taek Hong [1,2,*], Hyun Jin Park [1,2], Bo Kyung Kim [1,2], Hong Yul An [1,2], Jung Yoon Choi [1,2] and Hyoung Jin Kang [1,2,3]

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Meanwhile, biopsy results came back

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- ALK + Anaplastic Large T-Cell Lymphoma
- Stage II
- MDD positivity in peripheral blood

→ Treatment according to AIEOP-ALCL 99 protocol

After 10 days in the PICU…. (3 days of IgEV and 10 days of Anakinra)

Patient was trasnferred back to the onco-hematology ward

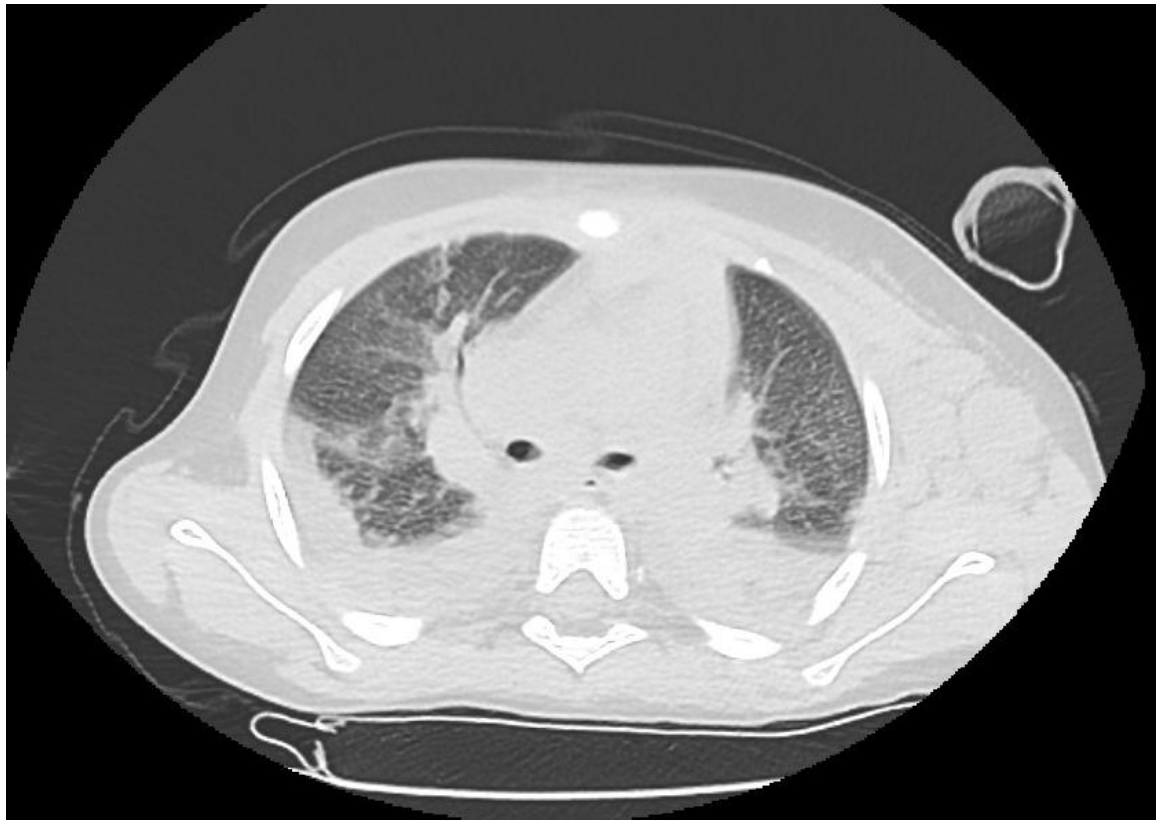
HLH was solved

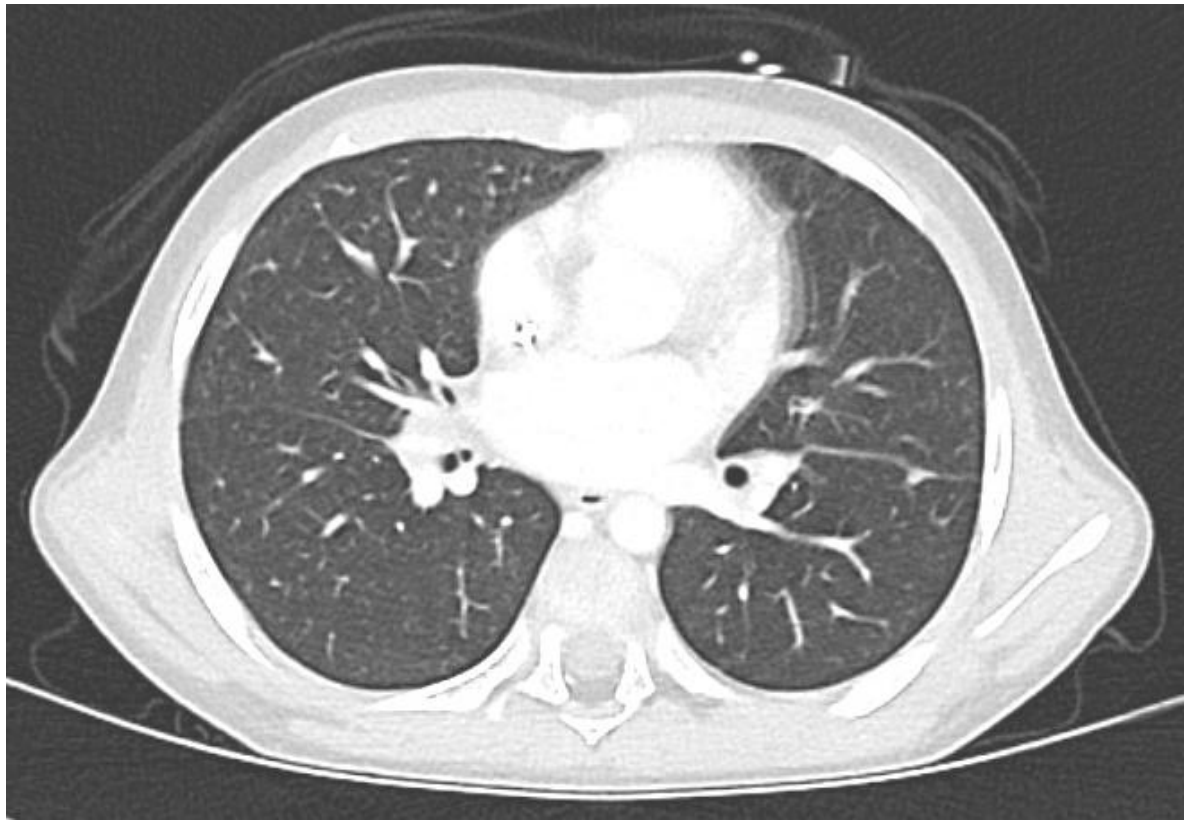
She was able to continue her cytostatic treatment as planned

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Re-evaluation

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INITIAL CHEST CT

CHEST CT AT RE-EVALUATION

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Re-evaluation

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Nevertheless, the patient had persistent MDD positivity

Immunophenotype at diagnosis: CD30+, ALK1 +, CD3 partially positive, CD2 partially positive, CD5-, CD7+, perforin+, CD20-, Ki67 80%.

TREATMENT RECEIVED SO FAR

Pre-phase | AM1 | BM1 | AM2 | BM2 | AM3 | BM3

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Question 3

What would you have done in terms of treatment?

1. Continue according to the protocol (3 more chemotherapy blocks)

2. Intensify treatment by adding immunotherapy

3. Intensify treatment with «stronger» chemotherapy

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MDD in ALCL: a tool for prognostic risk stratification

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MDD positivity shows persistence of molecular disease.

MDD evaluation may provide valuable prognostic information by helping identify higher risk patients.

Leukemia (2013) 27, 416–422
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www.nature.com/leu

ORIGINAL ARTICLE

Use of minimal disseminated disease and immunity to NPM-ALK antigen to stratify ALK-positive ALCL patients with different prognosis

L Mussolin[1,4], C Damm-Welk[2,4], M Pillon[1], M Zimmermann[2], G Franceschetto[1], K Pulford[3], A Reiter[2], A Rosolen[1,5] and W Woessmann[2,5]

Received: 2 February 2025 | Accepted: 1 May 2025
DOI: 10.1111/bjh.20154

REVIEW

Anaplastic large cell lymphoma in children and adolescents

Eric J. Lowe[1] | Wilhelm Woessmann[2]

Quantification of minimal disseminated disease by quantitative polymerase chain reaction and digital polymerase chain reaction for *NPM-ALK* as a prognostic factor in children with anaplastic large cell lymphoma

Christine Damm-Welk,[1*] Nina Kutscher,[1] Martin Zimmermann,[2] Andishe Attarbaschi,[3] Jutta Schieferstein,[1] Fabian Knörr,[4] Ilske Oschlies,[5] Wolfram Klapper[5] and Wilhelm Woessmann[1,4]

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Ferrata Storti Foundation

Haematologica 2020
Volume 105(8):2141-2149

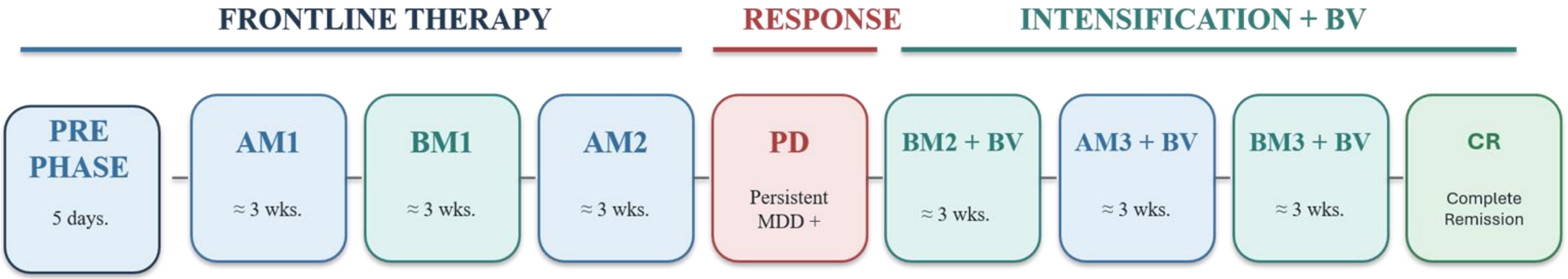
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What we did for our patient

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DIAGNOSIS

ALK+ ALCL
Stage II, MDD+



AM / BM

Alternated chemotherapy cycles.
~21 days/block.

PD

Persistent disease at re-evaluation
→ indicazione all'intensificazione.

BV

Brentuximab vedotin:
drug conjugated monoclonal antibody against CD30.

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What is the rationale for Brentuximab-Vedotin use

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- ALCL still has a high rate of relapse
- It has been showed that adding BV in frontline treatment for those who have persistent/high risk disease can improve the outcome without excessive toxicity

frontiers | Frontiers in Immunology

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Check for updates

OPEN ACCESS

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Brentuximab vedotin use in pediatric anaplastic large cell lymphoma

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CLINICAL TRIALS AND OBSERVATIONS | JULY 1, 2021

Brentuximab vedotin in combination with chemotherapy for pediatric patients with ALK+ ALCL: results of COG trial ANHL12P1

Clinical Trials & Observations

Eric J. Lowe, Anne F. Reilly, Megan S. Lim, Thomas G. Gross, Lauren Saguilig, Donald A. Barkauskas, Rui Wu, Sarah Alexander, Catherine M. Bollard

Check for updates

Blood (2021) 137 (26): 3595–3603.

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TAKE HOME MESSAGES

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- ALCL diagnosis can be challenging at onset. Persistent symptoms require further investigation, even when an infectious disease diagnosis appears plausible
- HLH is a potentially fatal presenting or early complicated manifestation of ALCL and should be recognized promptly
- MDD positivity may help to early identify higher risk patients
- Brentuximab-Vedotin represents a valid therapeutic option in patients with persistent disease