European Reference Network
for rare or low prevalence complex diseases

Network Paediatric Cancer (ERN PaedCan)

Management of a patient with refractory ALK+ anaplastic large cell lymphoma

Eda Ataseven & Laurence Brugières

ERN PaedCan – Young SIOPE webinar series

"Most challenging cases in paediatric oncology"

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COI Declaration

Eda Ataseven : no conflicts of interest to declare.

Laurence Brugières : consultant for TAKEDA

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Presentation

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A 13-year-old boy presented with fever for two weeks and enlarged cervical lymph nodes.

No past and family history.

Bilateral cervical, left supraclavicular painful, firm and fixed lymph nodes. Hepatomegaly.

WBC: 6 x 10^3 /µL

ANC: 3.4 x 10^3 /µL

Hb: 8.2 g/dL

plt: 127 x 10^3 /µL

LDH: 470 IU/L

ESR: 47 mm/h

USG: lymphadenitis?

Hospitalization, IV antibiotics

Viral markers (-), EBV DNA(-)

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2 days later:

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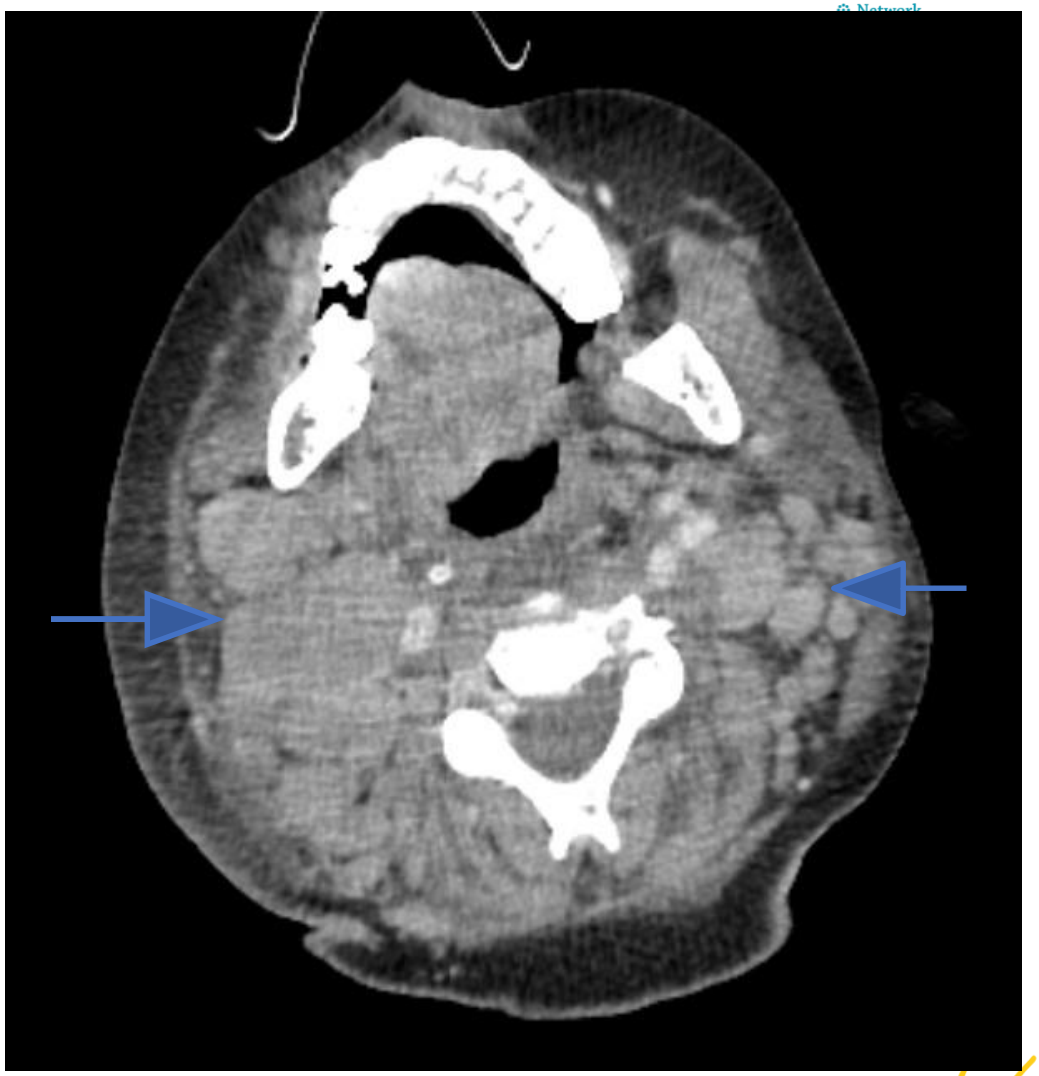
Progression in size of the lymph nodes and nodular lesions developed over the scalp. Fever persisted (39-40°C).



WBC: 5.4 x 10^3/µL
ANC: 3.5 x 10^3/µL

Hb: 6.9 g/dL

plt: 91 x 10^3/µL

LDH: 942 IU/L

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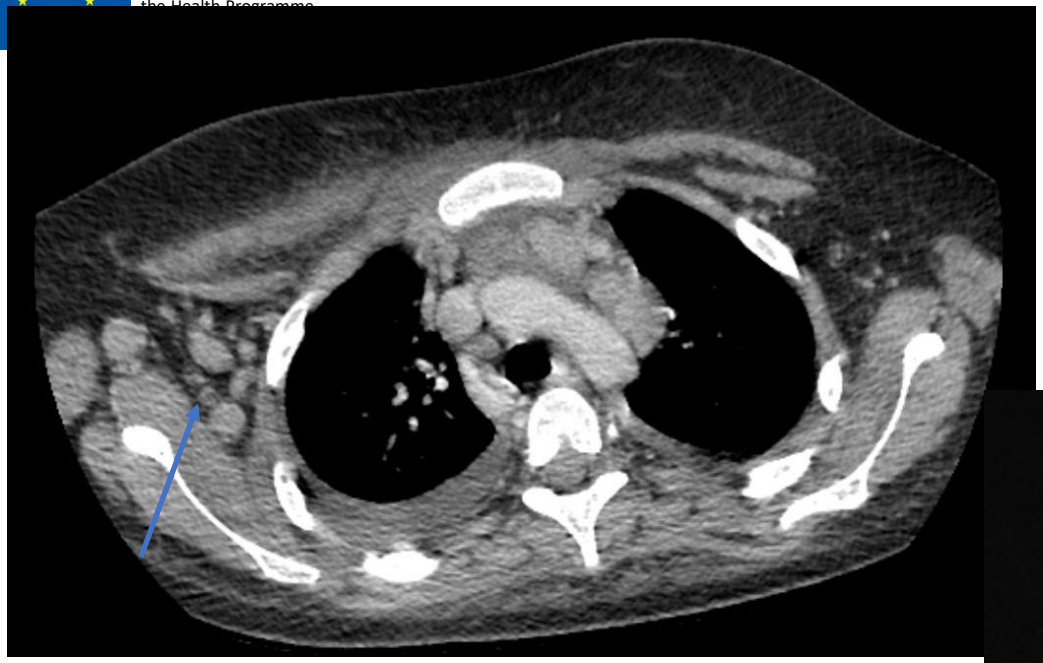

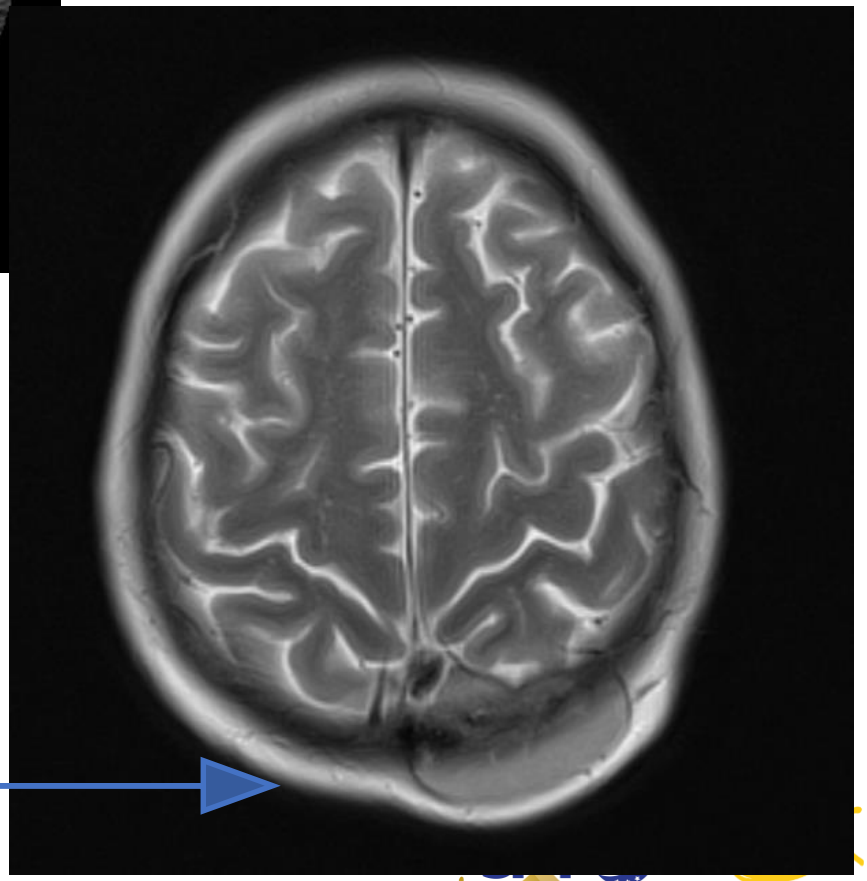

A lesion causing erosion in parietal bone and dural invasion.

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Bone Marrow: 15% blastic infiltration no hemaphagocytosis

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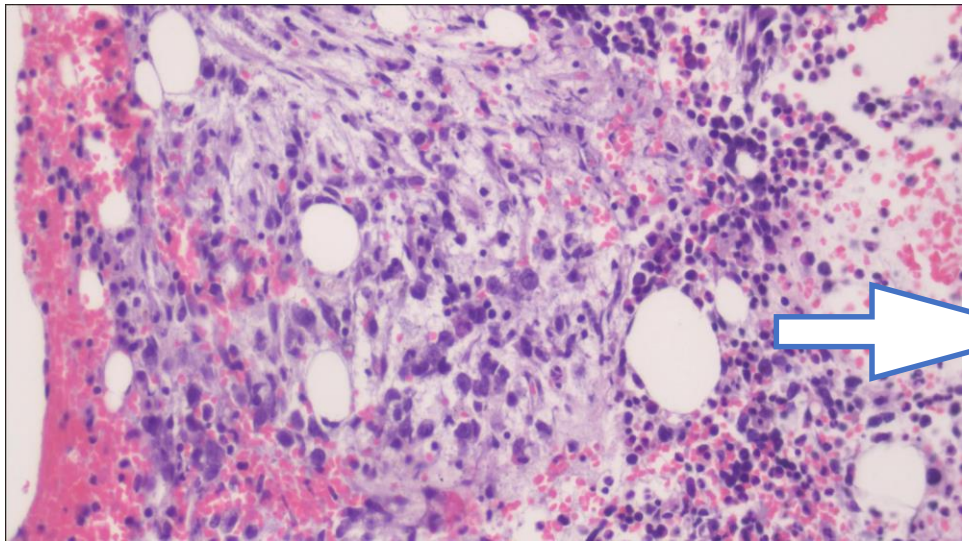

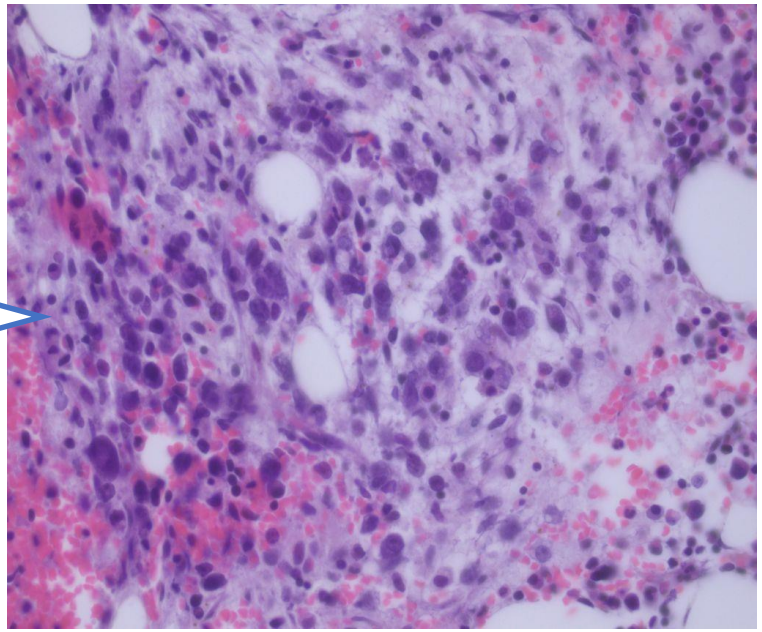

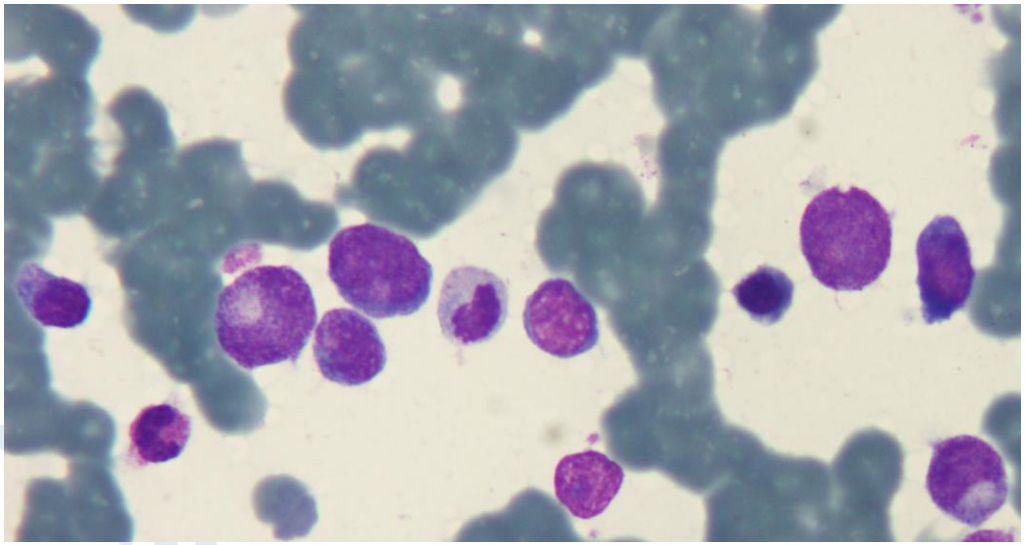

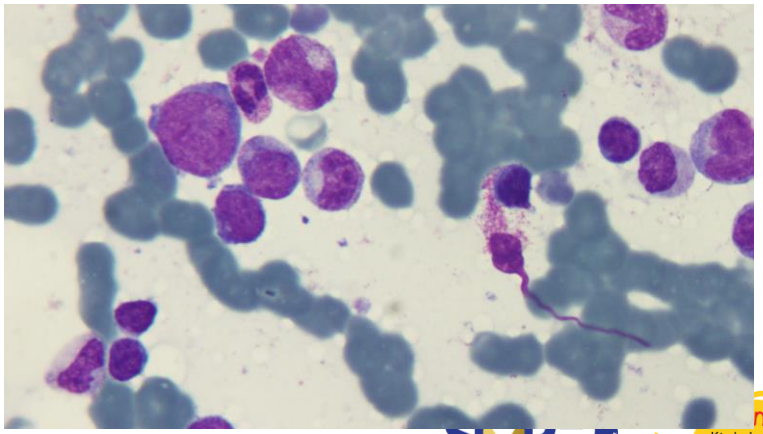

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Lymph node histopathology

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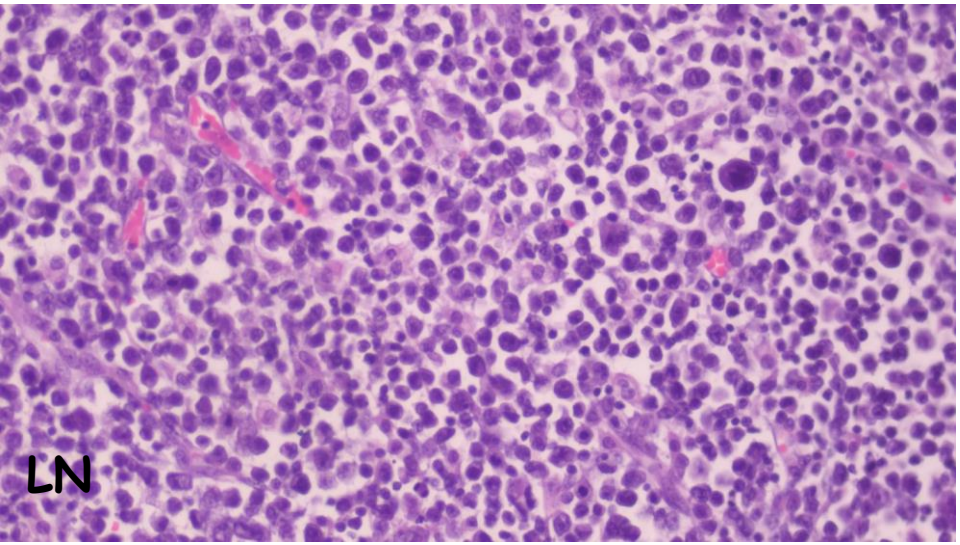

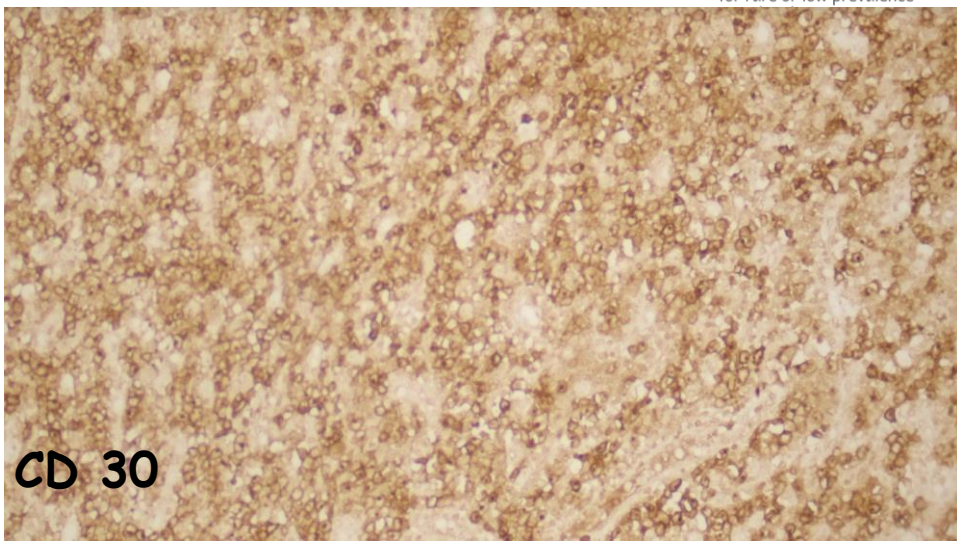

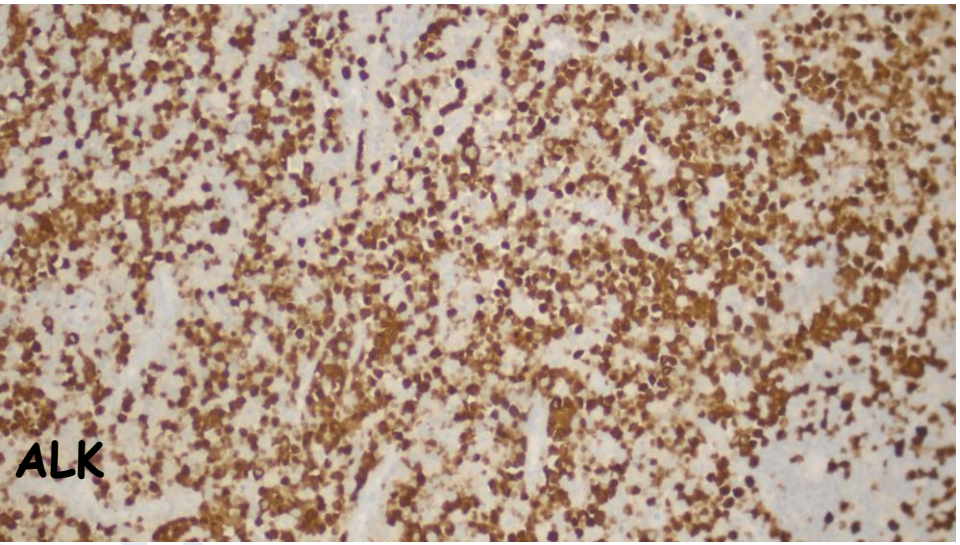

ALK (+) anaplastic large cell lymphoma, small cell type

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ALK (+) ALCL

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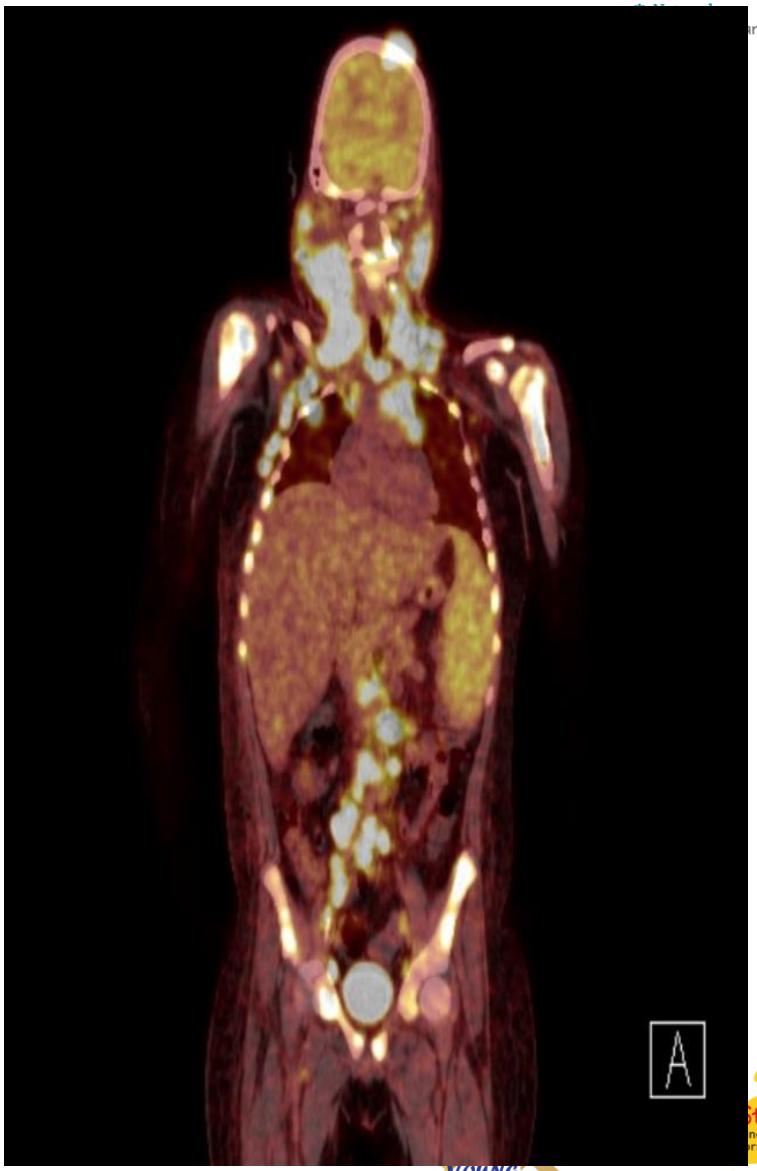
- multiple lymph nodes (+)
- spleen (+)
- multiple bone (+)
- bone marrow (+)

- CSF cytology: (-)
- fever- B symptoms (+)



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Question:

1. Which is the most important prognostic factor in this patient can be related with poor prognosis?

- Visceral involvement
- Mediastinal involvement
- B symptoms
- Bone marrow involvement
- Histologic subtype

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Question

- Systemic ALK (+) ALCL
- **Problem:** CSF cytology benign (but dural invasion positive on Cranial MRI)

How would you classify this patient and what would be your proposal for the treatment?

- CNS negative, treatment like systemic ALCL
- CNS positive, treatment like CNS- positive mature B-NHL

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NHL-BFM 2012 protocol

Vorphase | **AAZ1** | **BBZ1**

Day 2:
Fever disappeared

Febrile neutropenia

Day 10:
End of AAZ1

Day 14:
Control USG:
Regression in all cervical lymph nodes

Day 25:
Persistent fever for 11 days, all bacterial-viral-fungal tests negative
Progression in cervical lymph nodes

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Is diagnosis really true??
Re-evaluation;

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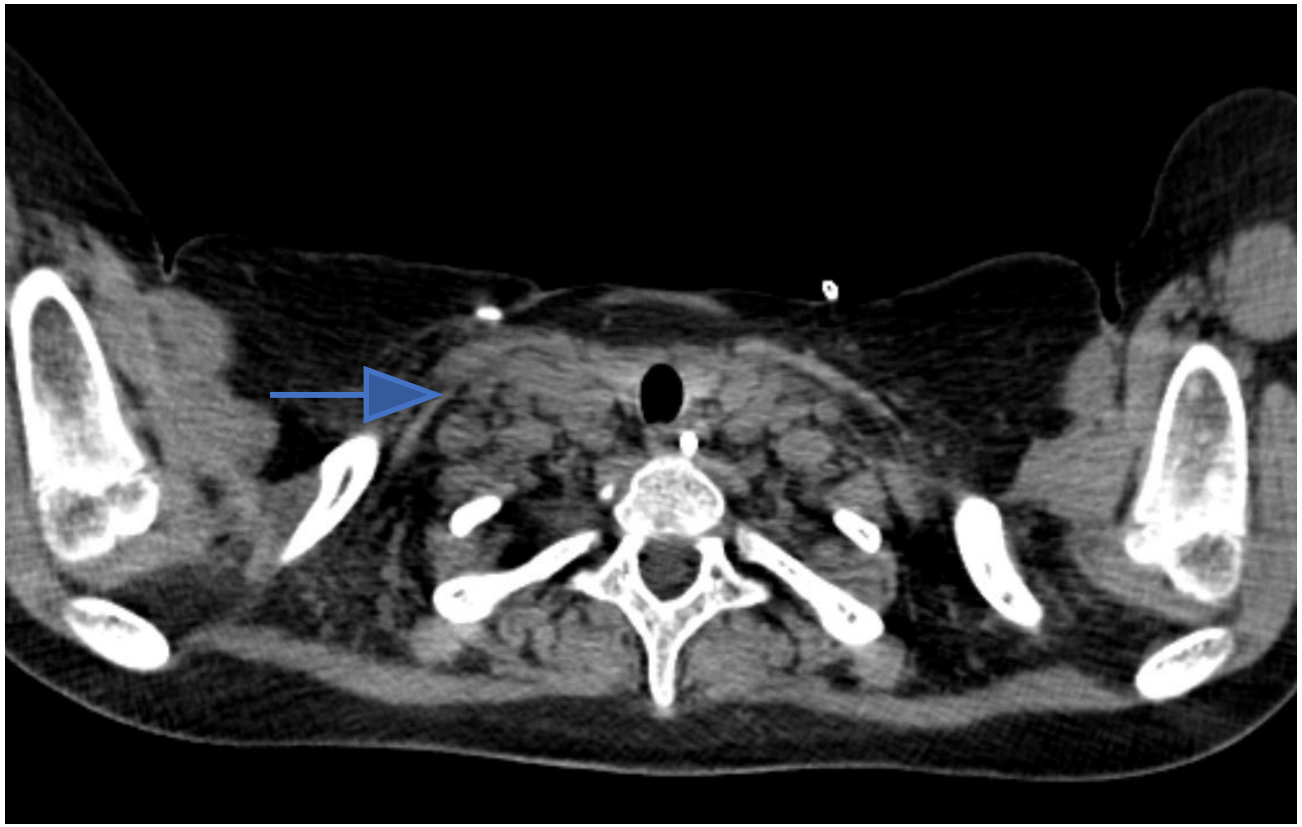

- **Radiology:** Progression in all lymph nodes.
- **Bone marrow aspiration:** Normal

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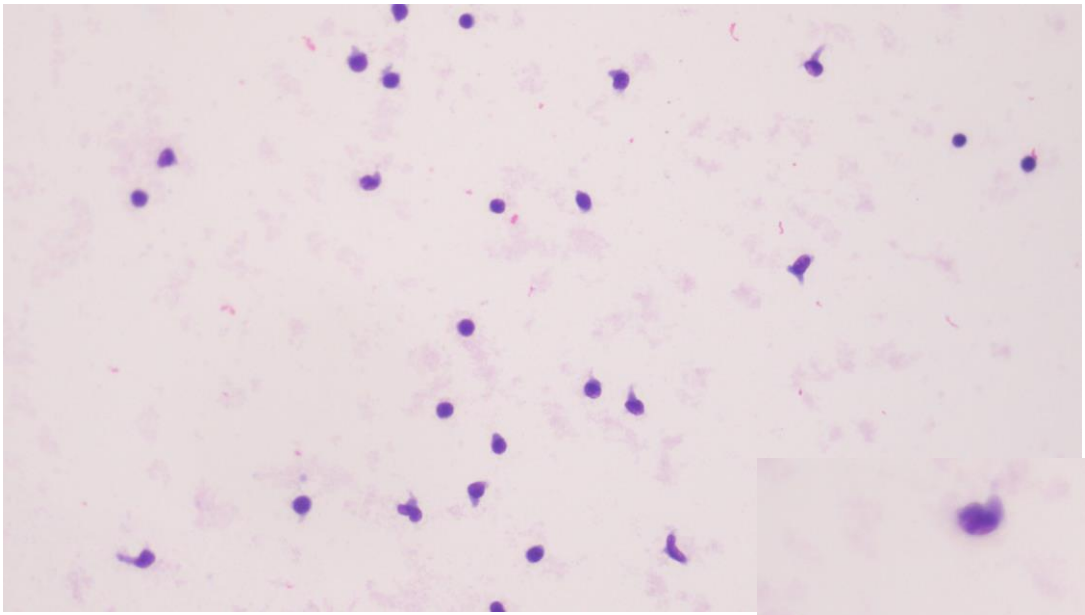
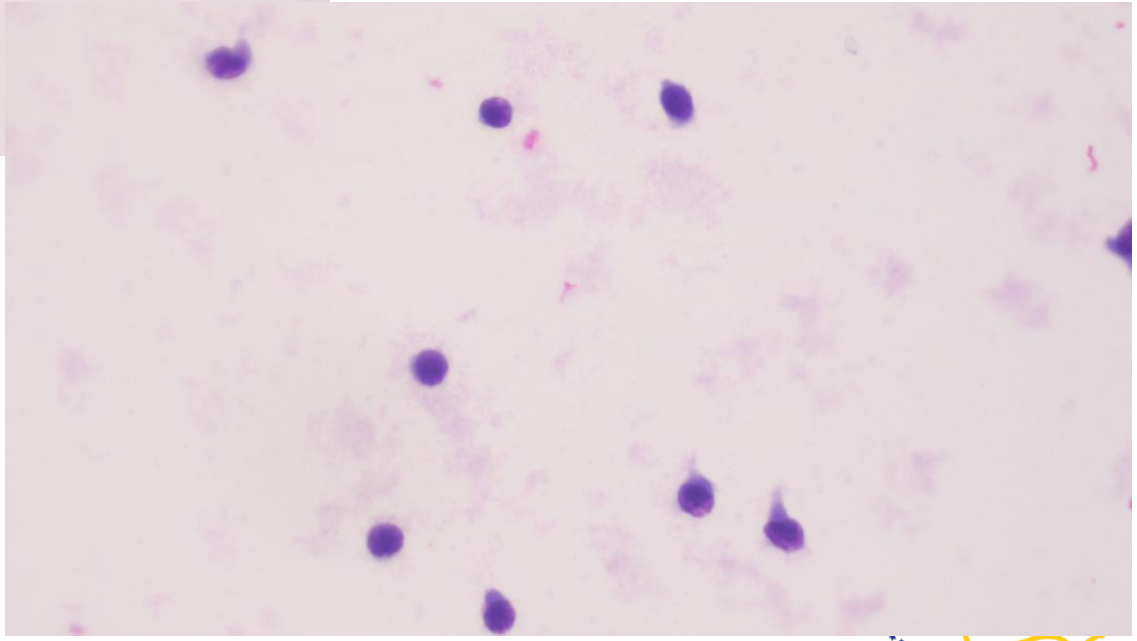


CSF: Malignant



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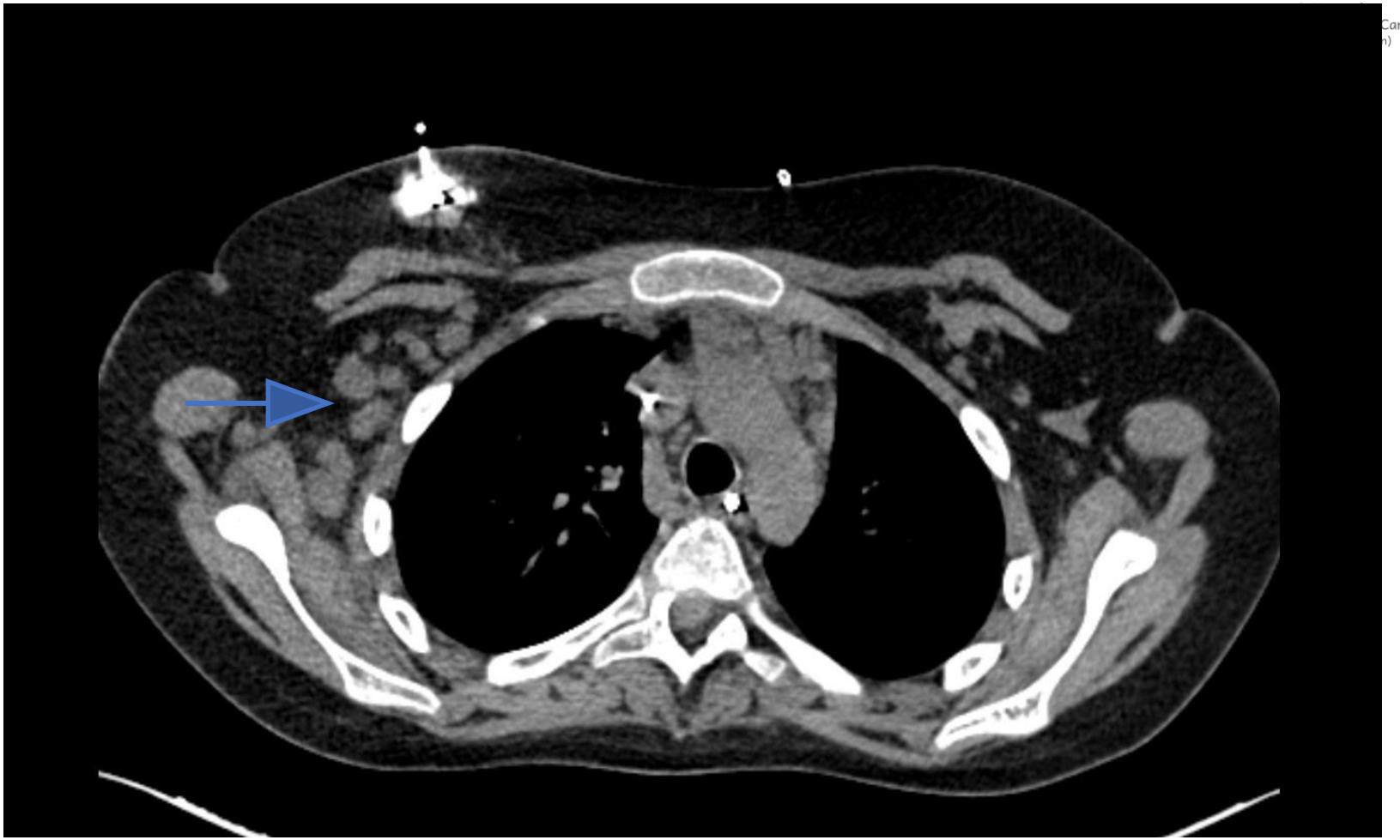

- Lymph node excision: ALK (+) ALCL

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Question:

What would be your treatment approach in this patient?

- Chemotherapy with vinblastine including regimens
- Chemotherapy and anti-CD 30
- ALK inhibitors
- High dose chemotherapy and stem cell transplantation
- All

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BBZ1 (Brentuximab vedotin (anti CD-30) added)

	individual dose	1	2	3	4	5	6
dexamethasone		● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●
Brentuximab vedotin		■					
doxorubicin					●	●	
methotrexate (MTX)		●					
folinic acid			42	48 54			
cyclophosphamide			●	● ●	● ●		
MTX/ARA-C/PRED i.th.			●		●		●

CSF (+)

BMT board:
Allogenic BMT scheduled

Fever disappeared

Regression in lymph nodes

CC block with Brentuximab vedotin

dexamethasone		● ● ●	● ● ●	● ● ●	● ● ●	● ● ●
Brentuximab vedotin		■				
cytarabine (ARA-C)		● ●	● ●			
etoposide (VP-16)				● ●	● ●	●
MTX/ARA-C/PRED i.th.						●

CSF (-)

SIOPE

St. Anna Kinderkrebs Forschung

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After CC block therapy:

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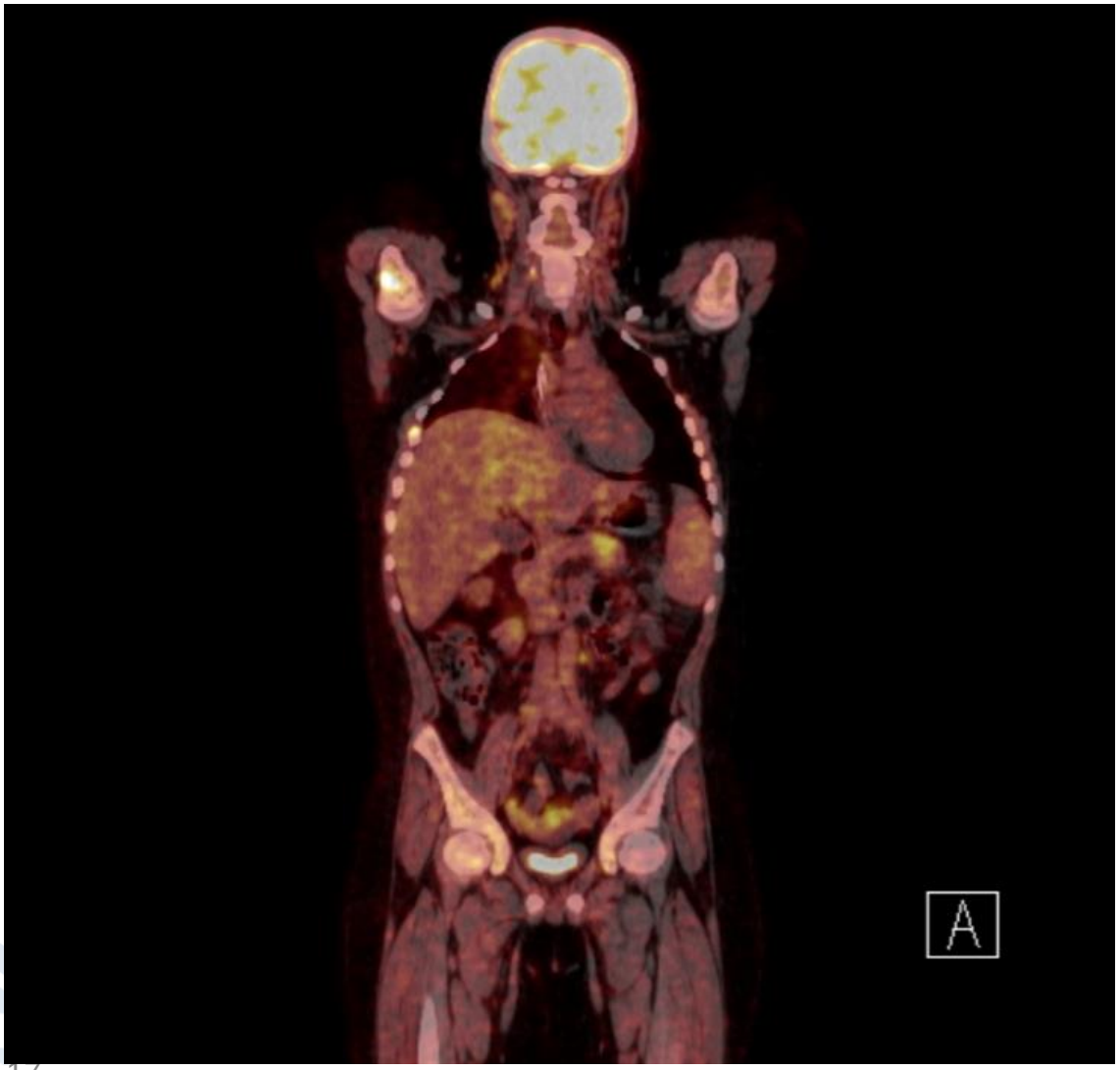

BMT board:
Allogenic BMT as soon as possible. No matched related donor. Unrelated donor search started.

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Four days after PET-CT:

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Fever, enlargement in cervical lymph nodes

AAZ2 with Brentuximab vedotin

dexamethasone		●●●	●●●	●●●	●●●	●●●	●●●
Brentuximab vedotin							
cytarabine (ARA-C)					● ●	● ●	
etoposide (VP-16)					●	●	
methotrexate (MTX)		●					
folinic acid			42	48 54			
ifosfamide			●	● ●	● ●		
MTX/ARA-C/PRED i.th.			●				●

ALK inhibitors

New treatment options?

fever Ø
lymph node regression

CSF (-)

Bone marrow aspiration:
POSITIVE FOR TUMOR CELLS

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10 days after AAZ2 + BV therapy--> fever + cervical lymphadenopathy

BV 1. day
Dexamethasone 1-5 days
Crizotinib
IT treatment(triple)

Day 3: Fever disappeared, regression in lymph nodes

Week 4:
PET CT: Regression in all lymph nodes, bone marrow and bone lesions
Bone marrow aspiration: Normal
CSF: Benign

Remission--> transferred to the transplantation unit

Universitätsklinikum Münster

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- Bone marrow and CSF in remission.
- Crizotinib--> Brigatinib

Dexamethasone 1-5 days
Brigatinib
IT treatment (triple)

- ALK MRD was negative with ALK inhibitors.
- Allo SCT performed (conditioning regimen: TBI + etoposid +ATG).
- Now, he is doing well (post-transplant 5 months) and in remission.

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Take home messages

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- Several factors have been shown to be associated with a higher risk of treatment failure.

  Most important ones are:

  - CNS involvement
  - detection of the ALK fusion in blood and/or bone marrow (MRD)
  - histologic subtype including a small cell and/or a lymphohistiocytic component .

- There are many options for the treatment of relapsed/refractory ALCL and most patients survive even after several relapses. New targeted therapies (especially with ALK inhibitors) have improved the response rate of such patients.

- Allo-SCT has been proven to be curative.

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Thank you very much for your attention.