European Reference Network
for rare or low prevalence complex diseases

Network Paediatric Cancer (ERN PaedCan)

15.10.2025

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Expert: Caroline Hutter

A severe case of refractory secondary lymphohistiocytosis

Moderation: Andishe Attarbaschi

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COI declaration

- No conflict of interest

ADMISSION

- Girl, 13 years old
- April 2023
- History: prolonged fever, splenomegaly
- Family history:
- parents, both healthy (father of Arabic origin, mother was Romanian)
- 1 younger sister, 3 years of age, healthy
- 1 younger sister, deceased under 1 year of age due to plurimalformative syndrome

CLINICAL EXAMINATION

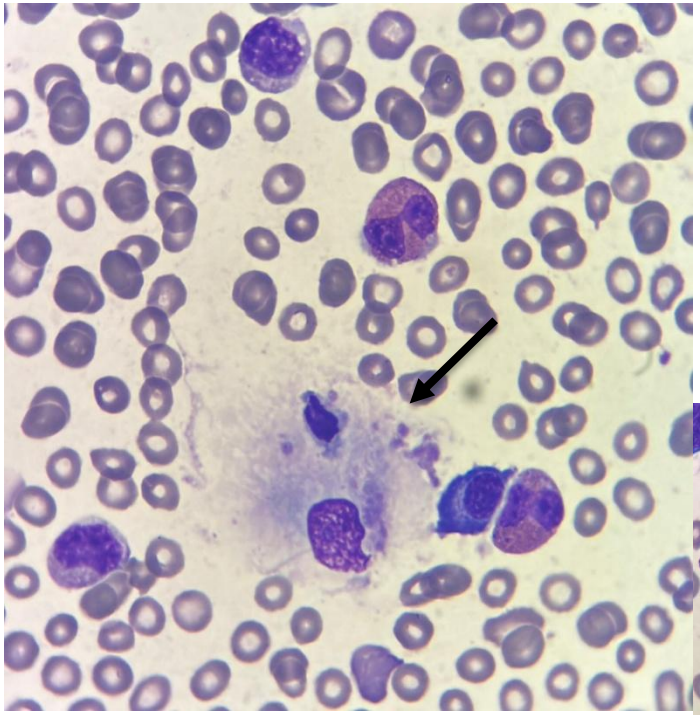
- Splenomegaly
- No adenopathies
- No other signs of disease

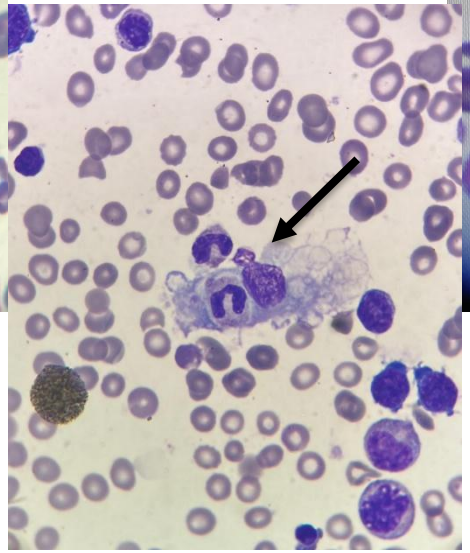
LABORATORY

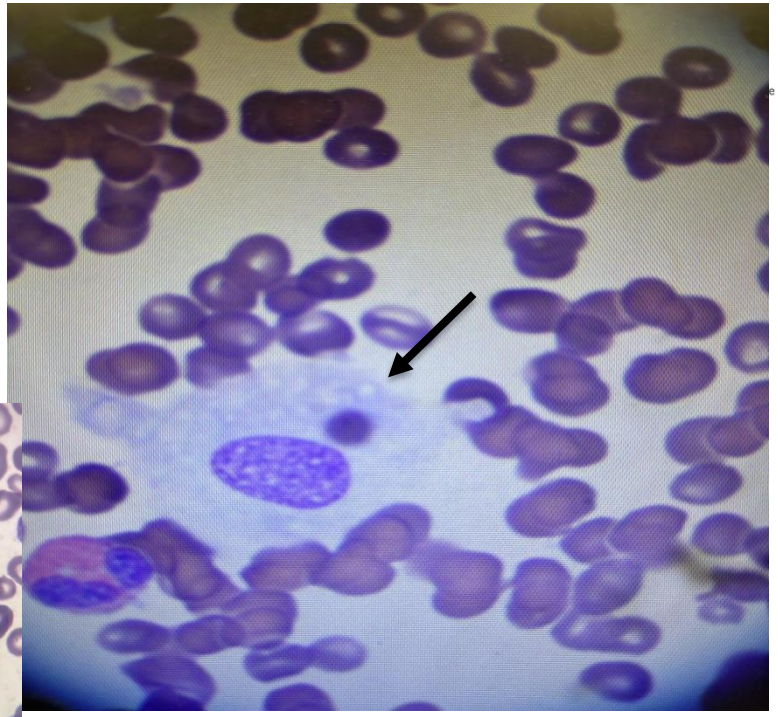
CBC COUNT:

- WBC: 1440/mm³
- Neutrophils: 700/mm³
- Hb: 8.3 g/dl
- Ht: 25.5%
- PLT: 68.000/mm³

- Fibrinogen 195 mg/dl
- Ferritin 1255 ng/ml
- Triglycerides 445mg/dl
- IL-2 Receptor >7500U/ml







VIRAL TESTS

- EBV IgM- negative
- EBV IgG – positive (high titer for EBNA)
- CMV – negative
- Toxoplasma- negative
- HIV – negative
- HVB, HVC- negative

OTHER TESTS

- Complement C3, C4 – within normal range
- ANA – negative
- DS-DNA – negative
- Rheumathoid factor- negative
- Genetic testing for HLH –in progress

HLH 2004 DIAGNOSTIC CRITERIA

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The diagnosis of HLH can be established if Criterion 1 or 2 is fulfilled.
1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH fulfilled (5 of the 8 criteria below) Fever Splenomegaly Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood) Hemoglobin <90 g/L (hemoglobin <100 g/L in infants <4 wk) Platelets <100 × 10^9/L Neutrophils <1.0 × 10^9/L Hypertriglyceridemia and/or hypofibrinogenemia Fasting triglycerides ≥3.0 mmol/L (ie, ≥265 mg/dL) Fibrinogen ≤1.5 g/L Hemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy. Low or no NK cell activity (according to local laboratory reference) Ferritin ≥500 μg/L sCD25 (ie, soluble IL-2 receptor) ≥2400 U/mL

If hemophagocytic activity is not proven at the time of presentation, further search for hemophagocytic activity is encouraged. If the bone marrow specimen is not conclusive, material may be obtained from other organs. Serial marrow aspirates over time may also be helpful. The following findings may provide strong supportive evidence for the diagnosis: spinal fluid pleocytosis (mononuclear cells) and/or elevated spinal fluid protein and histological picture in the liver resembling chronic persistent hepatitis (biopsy). Other abnormal clinical and laboratory findings consistent with the diagnosis are cerebromeningeal symptoms, lymph node enlargement, jaundice, edema, skin rash, hepatic enzyme abnormalities, hypoproteinemia, hyponatremia, and elevated very low-density lipoprotein (VLDL↑)/low high-density lipoprotein (HDL↓).

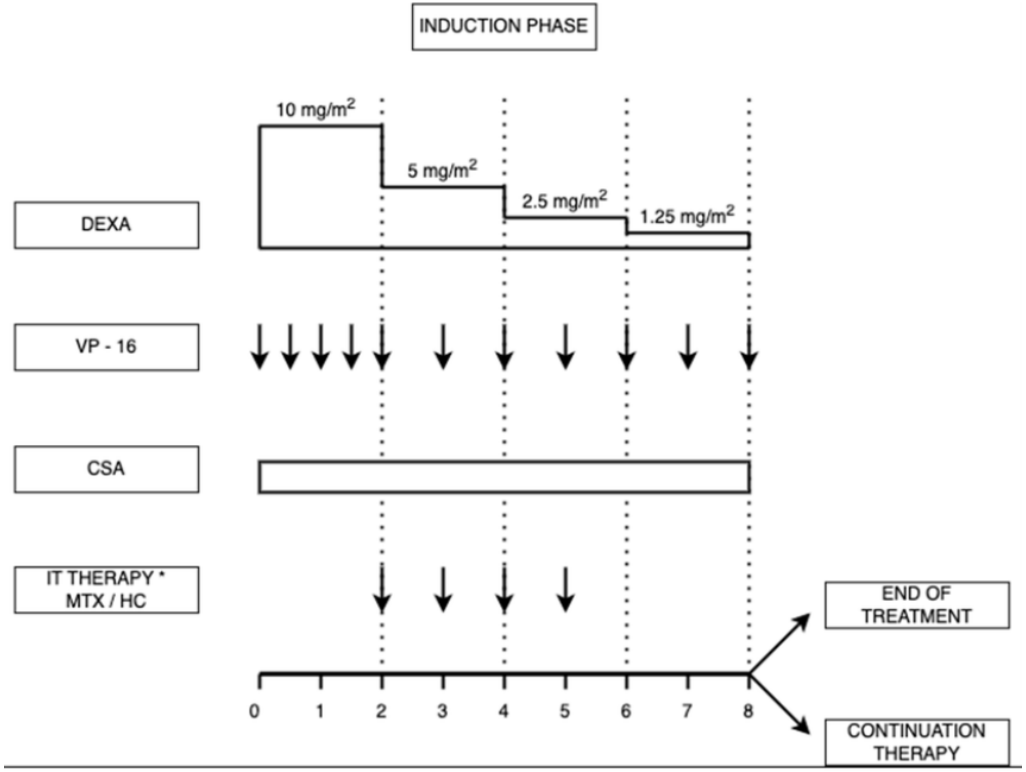
Question 1

Would you consider the diagnosis of HLH and treat by protocol?

A. YES

B. NO

HLH-2004 INDUCTION



FIRST TWO WEEKS

- Improvement of all HLH parameters, she had no fever, splenomegaly decreased

CBC COUNT:

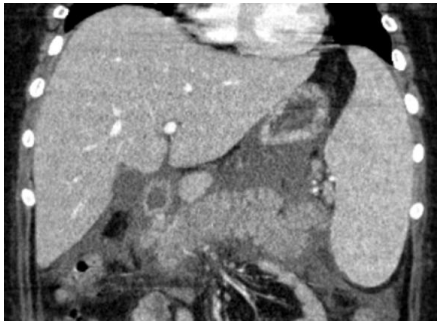
- WBC: 1900/mm³
- Neutrophils: 1500/mm³
- Hb: 8.9 g/dl
- Ht: 25.5%
- PLT: 118.000/mm³
- Ferritin 834 ng/ml
- Triglycerides 119mg/dl

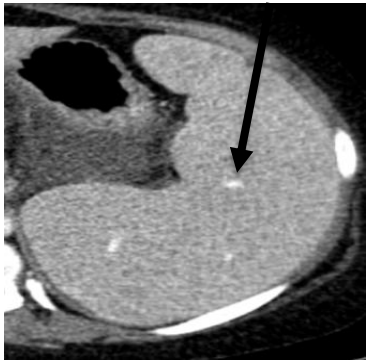
AFTER THE 4th VP16 ADMINISTRATION

Severe hematological toxicity
Fever
Keratoconjunctivitis
Sepsis parameters with cardiac involvement (myocarditis)

CBC COUNT:
WBC: 520/mm³
Neutrophils: 210/mm³
Hb: 7.9 g/dl
PLT: 61.000/mm³

- Ferritin 660 ng/ml
- Triglycerides 99mg/dl
- Fibrinogen 139 mg/dl
- C reactive protein 11.88mg/dl (Normal value <0.5mg/dl)
- Positive procalcitonine
- Cultures negative





Splenic granulomas (systemic candidemia)

CLINICAL COURSE

- Caspofungin intravenously (21 days)
- Continuation with oral Voriconazole
- Broad-spectrum antibiotics
- Local ophthalmic treatment
- Supportive care

CLINICAL COURSE

HLH TREATMENT WAS RETAKEN WITH REDUCED DOSAGE TO 50%

INDUCTION THERAPY WAS FINISHED

HLH PARAMETERS:

- **CBC COUNT:**

  WBC: 9000/mm³

  Neutrophils: 7000/mm³

  Hb: 11.3 g/dl

  PLT: 177.000/mm³
- **Ferritin** 1500 ng/ml (multiple blood transfusions)
- **Triglycerides** 150mg/dl
- **Fibrinogen** 222 mg/dl
- **IL-2 Receptor**: 1025U/l

CBC COUNT:
WBC: 1440/mm³
Neutrophils: 700/mm³
Hb: 8.3 g/dl
PLT: 68.000/mm³

Fibrinogen 195 mg/dl
Ferritin 1255 ng/ml
Triglycerides 445mg/dl
IL-2 Receptor >7500U/ml
Bone marrow involvement

CBC COUNT:
WBC: 1900/mm³
Neutrophils: 1500/mm³
Hb: 8.9 g/dl
PLT: 118.000/mm³

Ferritin 834 ng/ml
Triglycerides 119mg/dl

CBC COUNT:
WBC: 520/mm³
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Fibrinogen 139 mg/dl
Ferritin 660 ng/ml
Triglycerides 99mg/dl

CBC COUNT:
WBC: 9000/mm³
Neutrophils: 7000/mm³
Hb: 11.3 g/dl
PLT: 177.000/mm³

Complications

Fibrinogen 222 mg/dl
Ferritin 1500 ng/ml (multiple blood transfusions)
Triglycerides 150mg/dl
IL-2 Receptor: 1025U/l

GENETIC TESTING

TEST: WHOLE EXOME SEQUENCING

REASON FOR TESTING: Hemophagocytic Lymphohistiocytosis.

RESULT **NEGATIVE**

ABOUT THIS TEST: This test looked for sequence variations that could explain the patient's phenotype.

PRIMARY FINDINGS:

- no pathogenic or likely pathogenic variants were identified in genes associated with HLH.

CARRIER STATUS:

- heterozygous for a likely pathogenic variant in the PEX6 gene

Question 2

Would you continue HLH-2004 protocol or stop at this point with treatment and monitor?

A. CONTINUE

B. STOP

- Due to severe complications, but with partial remission of HLH and the exclusion of genetic HLH we decided to monitor and not continue with weeks 9-24 of the HLH-2004 protocol

CLINICAL COURSE

- After 1 week – moderate pancytopenia, higher levels of IL-2 soluble receptor and ferritin – active disease

CBC COUNT:

WBC: 2370/mm³

Neutrophils: 210/mm³

Hb: 8.4 g/dl

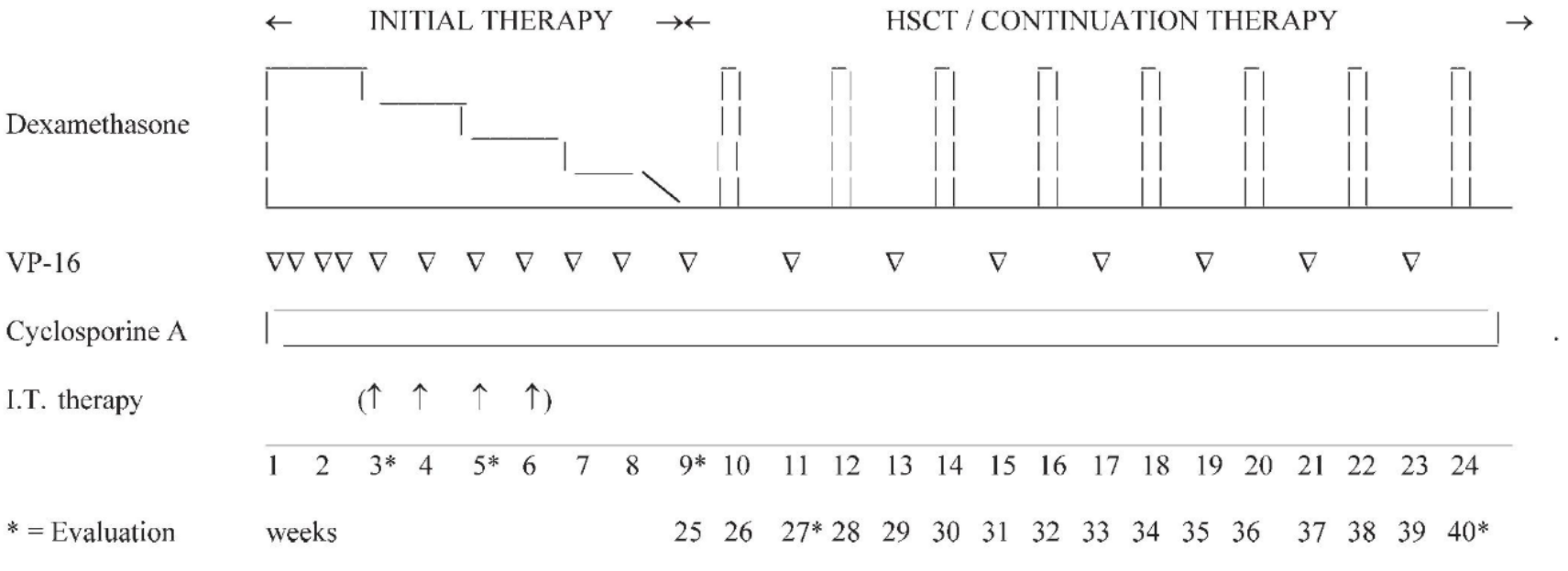
PLT: 87.000/mm³

Ferritin 4849 ng/ml

Triglycerides 250mg/dl

Fibrinogen 195 mg/dl

IL-2 Receptor >7500U/l


← INITIAL THERAPY →← HSCT / CONTINUATION THERAPY →
Dexamethasone
VP-16
Cyclosporine A
I.T. therapy
(↑ ↑ ↑ ↑)
1 2 3* 4 5* 6 7 8 9* 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
* = Evaluation
weeks
25 26 27* 28 29 30 31 32 33 34 35 36 37 38 39 40*

- 75% of total amount

Low hematological parameters
Mild inflammatory syndrome
Mild hepatic toxicity
Smaller splenic granulomas

Prophylaxis with Trimethoprim/Sulfamethoxazole
Treatment with Voriconazole orally

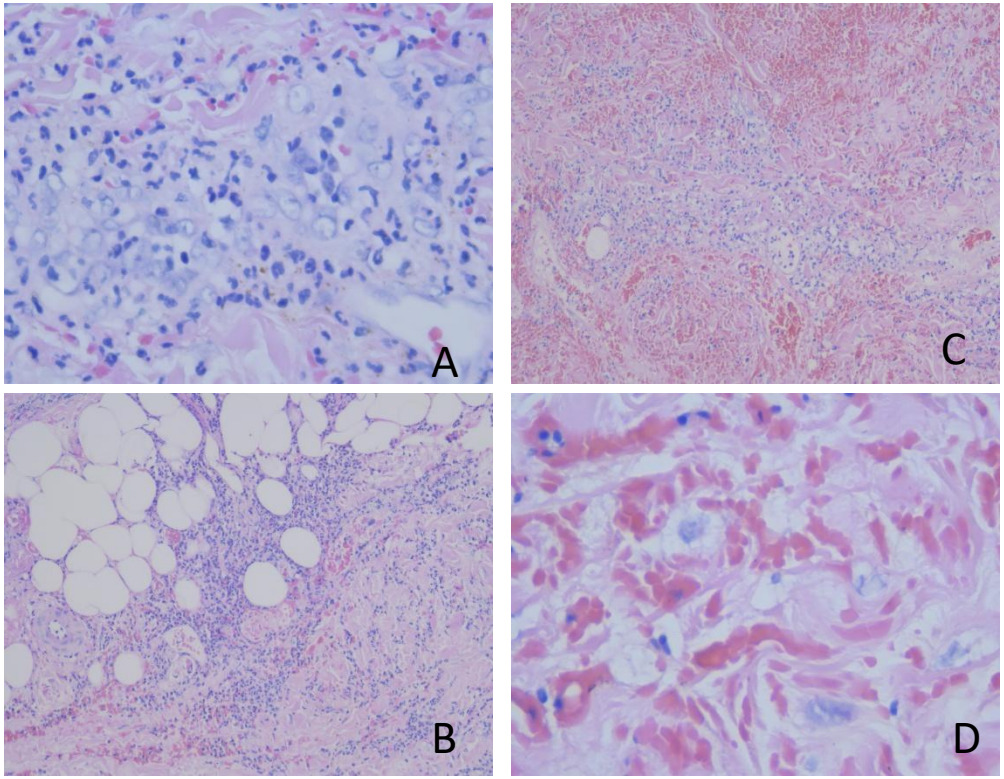
- Cutaneous vesicles with haemorrhagic aspect (PLT 108.000/mm3, coagulation profile within normal range)
- Lesions were biopsied

- Meropenem intravenously
- Acyclovir intravenously

No good clinical or biological evolution

- Clyndamicin, Colistin

Improvement of lesions



A: Derm with hemorrhage and inflammatory infiltrate (lymphocytes, PMN neutrophils and histiocytes)

B: Inflammatory infiltrate in the adipose tissue

C: Inflammatory infiltrate in derm

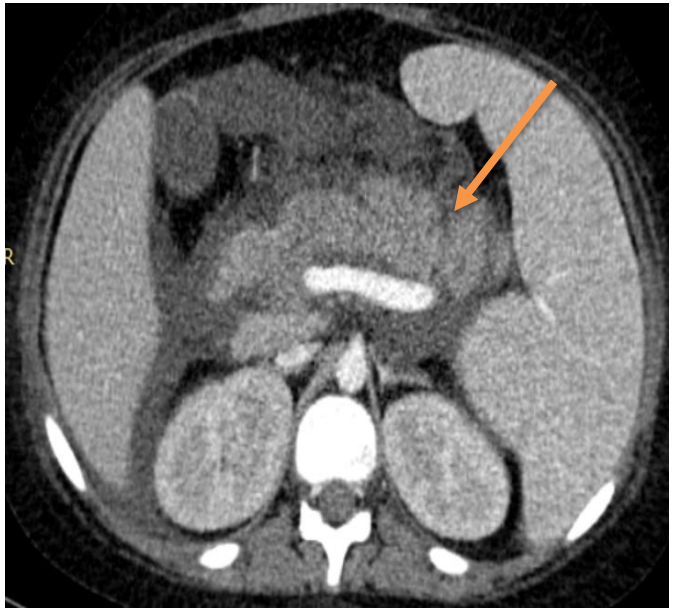
D: Histocytes in intimate contact with erythrocytes

EVOLUTION

- HLH treatment continued 75% of dosage

- Sudden onset of vomiting, severe abdominal pain

Acute pancreatitis



CBC count:
WBC: 6460/mm³
Neutrophils: 5860/mm³
Hb: 9.6 g/dl
PLT: 17.000/mm³
C reactive protein 6.73 mg/dl
Amylase: 1090 U/l
Lypase: 2612 U/l
Triglycerides: 360mg/dl
Ferritin >1500 ng/dl
Fibrinogen: 86 mg/dl
BUN: 109 mg/dl
Creatinine: 1.43mg/dl

ICU admission – hydration, albumin supplementation, parenteral nutrition, analgesics, broad-spectrum antibiotics + antifungal therapy, G-CSF

Stable disease

Question 3

- WHAT WOULD YOU DO NEXT?

A. Stop HLH treatment?

B. Continue with the same dosage?

C. Switch therapy for HLH to something else?

Anakinra – 10mg/kg/day

Good evolution of hematological parameters

Good general status

BEFORE ANAKINRA

- WBC: 530/mm³
- Neutrophils: 360/mm³
- Hb: 7.1 g/dl
- PLT: 12.000/mm³

AFTER ANAKINRA

- WBC: 3620/mm³
- Neutrophils: 2470/mm³
- Hb: 8.3 g/dl
- PLT: 40.000/mm³

- Sudden onset of fever and shivers
- Jaundice with fulminant hepatic failure
- Cough

GOT 385 U/L

GPT 566 U/L

Total bilirubin 23mg%

Direct bilirubin 19mg%

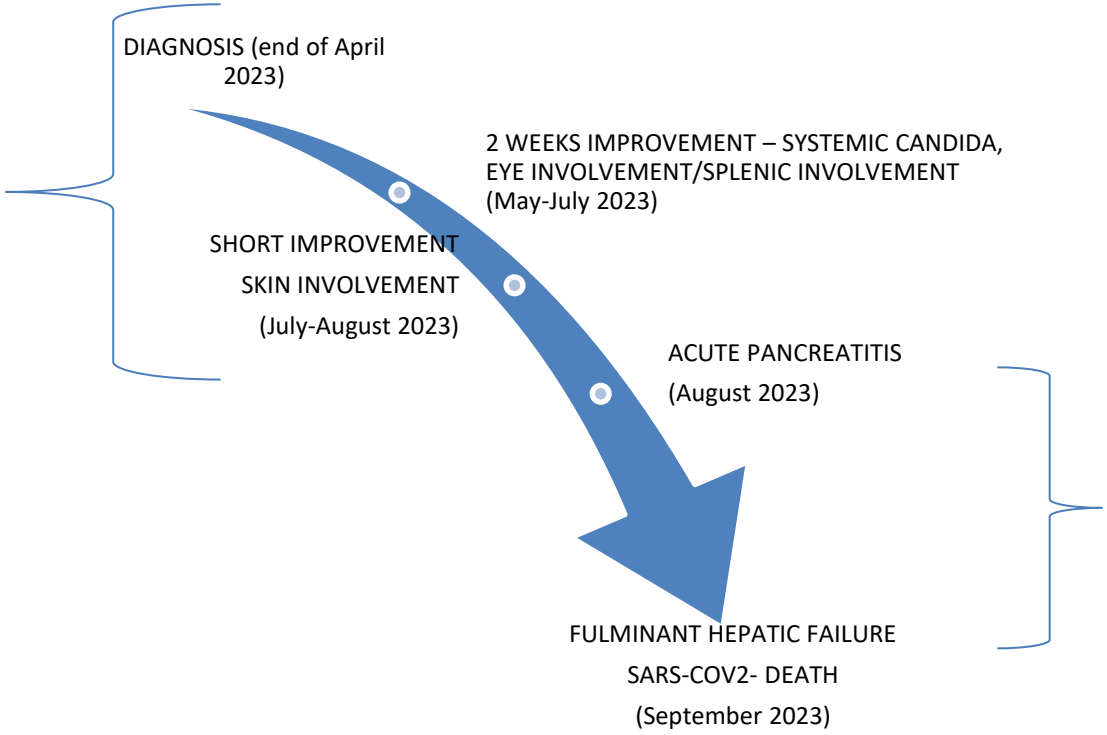
TQ 28 sec

INR 2

POSITIVE SARS-COV2

- ICU admission due to severe respiratory insufficiency
- Remdesivir not administered due to hepatic failure
- Deterioration - death

HLH 2004 PROTOCOL



HIGH-DOSE ANAKINRA

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DISCUSSION

Funded by the European Union's Health Programme

Take home messages

- Very delicate balance between disease and complications due to immunesupression
- No concrete cause, can lead to a difficult therapeutical decision and poor prognosis