ESIM 2011

Klinikum Bremen-Mitte, Germany
Intensive Care Unit

Dr. Christiane Piepel

Presentation at the ICU

69-year old male patient

- drowsiness, confusion, hypothermia (34.3°C)
- progressive dyspnea at rest (respiratory frequency 25/min, oxygen saturation 94% with 4 l of oxygen), peripheral cyanosis
- hypotension (70/40 mmHg), 70 bpm
- decreasing urinary output

Physical examination:

- mucous membranes dry
- thorax: bilateral moist rales auscultated over the lungs, regular heart beats
- abdomen: tender, poor bowel sounds in all quadrants, no pain on palpation, hepatomegaly (palpable 10 cm under the costal arch), ascites
- lower limbs: non-pitting edema, non-eminent exanthema on the right
- paper skin, multiple hematomas, teleangiectasias around the thorax

Previous history

- ***Six months ago:*** healthy and active, alcohol consumption 1-2 beer per day, hypothyreoidism (substituted with thyroxine).
- painful induration and swelling of subcutaneous tissue in the lower abdomen, scrotum, penis; indurations and swellings in the arms
- weight loss (10 kg in 6 months)
- edema predominant in the legs
- several admittances in peripheral hospitals: phlegmone, pneumonia, alcoholic cirrhosis. No malignancies found.

- ***3 months ago:*** lupus panniculitis, lupus erythematodus retinopathy. Improvement with prednisolone and hydroxychloroquine. No SLE.

- ***10 days ago***: referral to a high level hospital.
- GP: liver cirrhosis, malignancy, hemochromatosis?
- erysipelas (lower limb, right), treatment with ampicillin/ sulbactam for 8 d

Hypothesis

- SIRS
- sepsis (e.g. pneumonia, phlegmone, erysipelas, bacterial peritonitis)
- cardiogenic shock – myocardial infarction, heart failure
- autoimmune disease, e.g. systemic lupus erythematosus
- advanced stage liver disease, e.g. alcoholic cirrhosis, hemochromatosis, viral hepatitis
- malignancy
- immunodeficiency syndrome, e.g. HIV

Laboratory results

Hyponatremia
↓ Sodium: 120 mmol/l (135-150)

Elevated liver enzymes, restricted liver function, coagulation
↑ GOT(AST): 208 U/l (<50)
↑ GPT (ALT): 115 U/l (<50)
↑ alkaline Phosphatase: 389 U/l (<128)
Bilirubin and GGT normal
↓ Albumin 8 g/l (35-52)
↑ aPTT 87 sec (<37)
↑ INR 2,0

Acute renal failure
↑ Creatinine: 1.39 mg/dl (<1.2)
↑ Urea nitrogen: 76 mg/dl (8-20)

Minor signs of infection:
White blood cell count: normal
↑ CRP 30 mg/l (<5)
↑ Procalcitonin 0.66 ug/l (<0.5)

Haemolytic , microcytic anemia
↓ hemoglobin 9.2 g/dl (13.5-17.5)
↑ LDH 929 U/l (<248)
reticulocyte count 1.1 % (0.6-1.6),

Thrombocytopenia
↓ platelets 17/nl (140-360)

↑ Ferritin 18605 ug/l (30-400)
↑ soluble IL-2 receptor (CD 25): 9546 U/ml (223-710)
↑ BNP 2185 ng/l (<194)

Diagnostics

- *chest X-ray*: pulmonary congestion, infiltrations in both lower lobes, pleural effusion on the right
- *abdominal ultrasound*: splenomegaly, hepatomegaly, aspect of micronodular cirrhosis
- *ascitic fluid*: white blood cells 122/ul (<5), red blood cells 435/ ul (<5), LDH 1171 U/l (<160). Sterile cultures.
- *blood smear*: anisocytosis, target cells, microcytic erythrocytes, small platelets, a few megathrombocytes, normal amount of leucocytes, altered granulation, little left shift, no activated monocytes
- *bone marrow biopsy*: hyperplasia of the hematopoiesis, hematopoietic maturation defects, active hemophagocytosis
- *dermatology*: leucocytoclastic vasculitis
- *serology*: no signs for acute viral infections, lupus, autoimmune antibodies, HFE-gen mutations

Further development

- the patient developed respiratory failure within 24 hours → intubation, mechanical ventilation
- septic shock → piperacillin+combactam+ciprofloxacin for 7 days, noradrenaline, prednisolone
- beginning of chemotherapy with Etoposide (induction with prednisolone)
  - pancytopenia 8 days later, white blood cells 0,54/nl (3.5-9.8), fever, septic shock
  - Ceftazidime + Fosfomycin for 8 days
  - G-CSF
- exitus 24 days after admission on the intensive care unit

Hemophagocytic lymphohistiocytosis

Pathophysiology:

cytokine dysfunction, uncontrolled accumulation, activation of T-Lymphocytes and macrophages in many organs

Etiology:

- *Genetic mutations*: mainly in children, often parental consanguinity
- *Infections*: viral (EBV, CMV, HIV, Herpes viruses, Parvovirus, HIV…), bacterial (Brucella, gram negative bacteria, TB…), fungal, parasites (Leishmania…)
- *Autoimmune disorders*: Still‘s disease, systemic lupus erythematodes, rheumatoid arthritis, systemic sclerosis…
- *Malignancies*: lymphomas, leukemias

Diagnosis

5 of the following criteria *or* 4 criteria + clinical suspicion:

1) fever (>38.5°C for at least 7 days)
2) splenomegaly
3) hemophagocytosis (bone marrow, spleen, lymph node)
4) cytopenia (≥ 2 cell lines)
5) hypertrigylceridemia or hypofibrinogenemia
6) serum ferritin level > 500 µg/l
7) soluble CD 25 (sIL-2 receptor) > 2400 U/ml
8) low or absent natural killer cell activity

Principles for treatment

- treatment of infections, transfusion of blood products...
- chemotherapy:
  - HLH-94 protocol: induction therapy with dexamethasone, chemotherapy with ciclosporin, etoposide, intrathecal methotrexate
  - new HLH 2004 protocol: with ciclosporine on day one
- curative allogeneic hematopoietic cell transplantation

Learning points

- Hemophagocytic lymphohistiocytosis is a very rare disease and caused by cytokine dysfunction.
- Important predisposing/ triggering factors: infections, autoimmune disorders, malignancies and genetic mutations (children)
- The disease usually mimics common infections, fever of unknown origin or hepatitis.
- Hemophagocytosis can be shown in liver, lymph nodes, bone marrow
- Treatment:
  - Immediate treatment is essential as the disease has a high mortality .
  - chemotherapy and consecutive (curative) hematopoietic cell transplantation


Thank you!