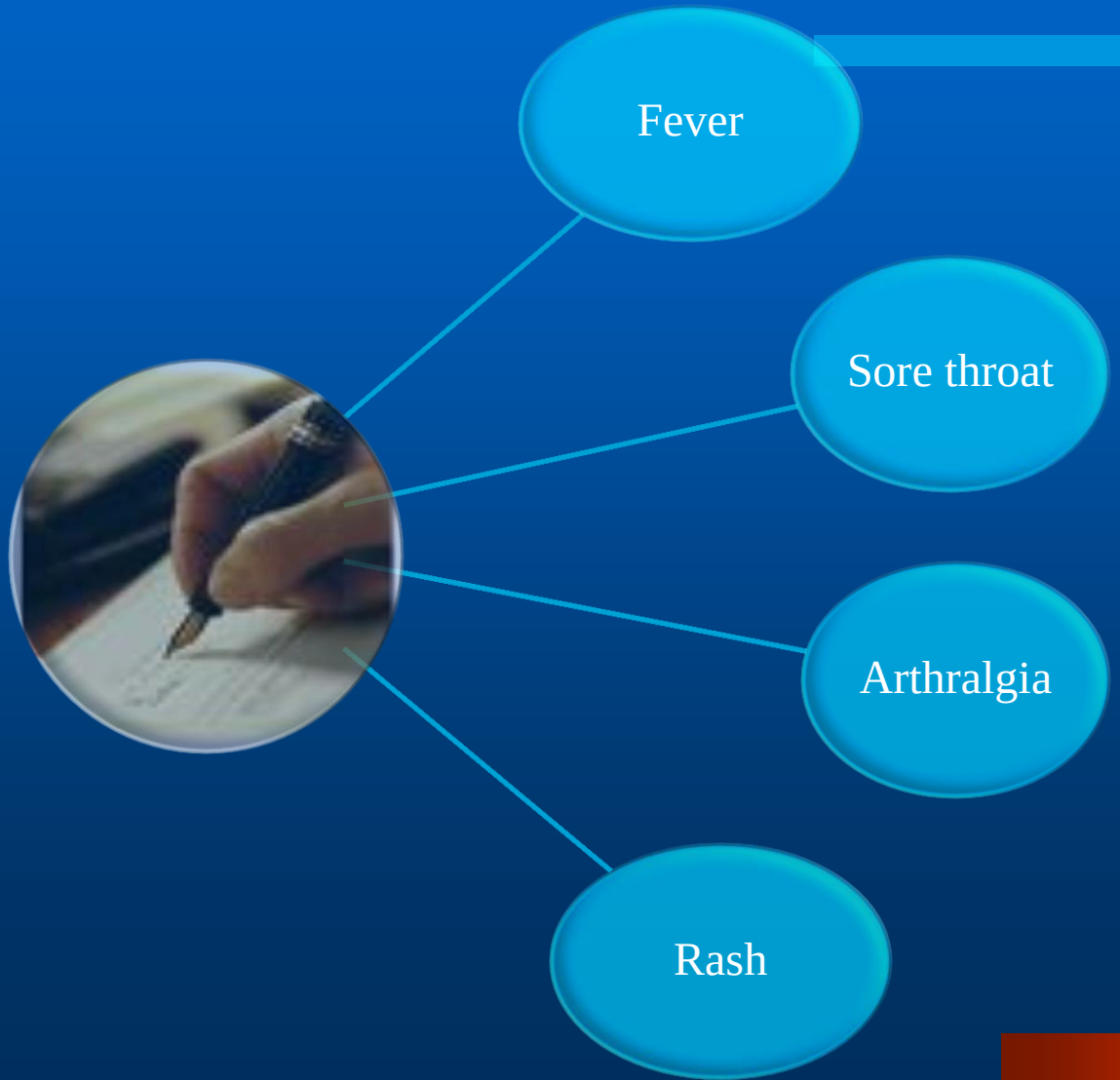
“Physician activation syndrome”

Does it exist ?

Tarek Saadi, MD
Liver Unit
Rambam - Health Care Campus
Haifa, Israel

A 19 years old previously healthy man



- These symptoms started 2 weeks before his admission
- He was treated with doxylin 100 mg/day for suggested infectious disease without any improvement in his symptoms

- He denied smoking tobacco, use of alcohol, herbal supplements or recreational drugs.
- He had no recent travel or sick contacts.
- There was no family history of autoimmune diseases.

Physical examination

- Temperature: 39.5 C
- Blood pressure:135/70
- Weight: 64

- Lungs, heart, abdomen: normal
- No lymphadenopathy or hepato-splenomegaly

- Macular rash was prominent on his face and extremities

- Joint examination: synovitis in the MCP'S, knees and ankles

Laboratory tests

WBC (x 10^3 /uL) **4-10.8**	13.7
Hgb (gr/dl) **13-17**	13.9
PLT (x 10^3 /uL) **130-350**	259

Creatinine (mg/dl) **0.2-1.3**	0.73
Ferritin (ng/ml) **15-300**	↑ 3481
ESR (mm/hr) **0-10**	↑ 80
CRP (ng/L) **0-5**	↑ 225

Albumin (g/dl) **3.5-5**	↓ 3.2
AST (u/L) **5-40**	41
ALT (u/L) **30-65**	↑ 90
GGT (u/L) **5-60**	↑ 96
ALP (u/L) **30-115**	95

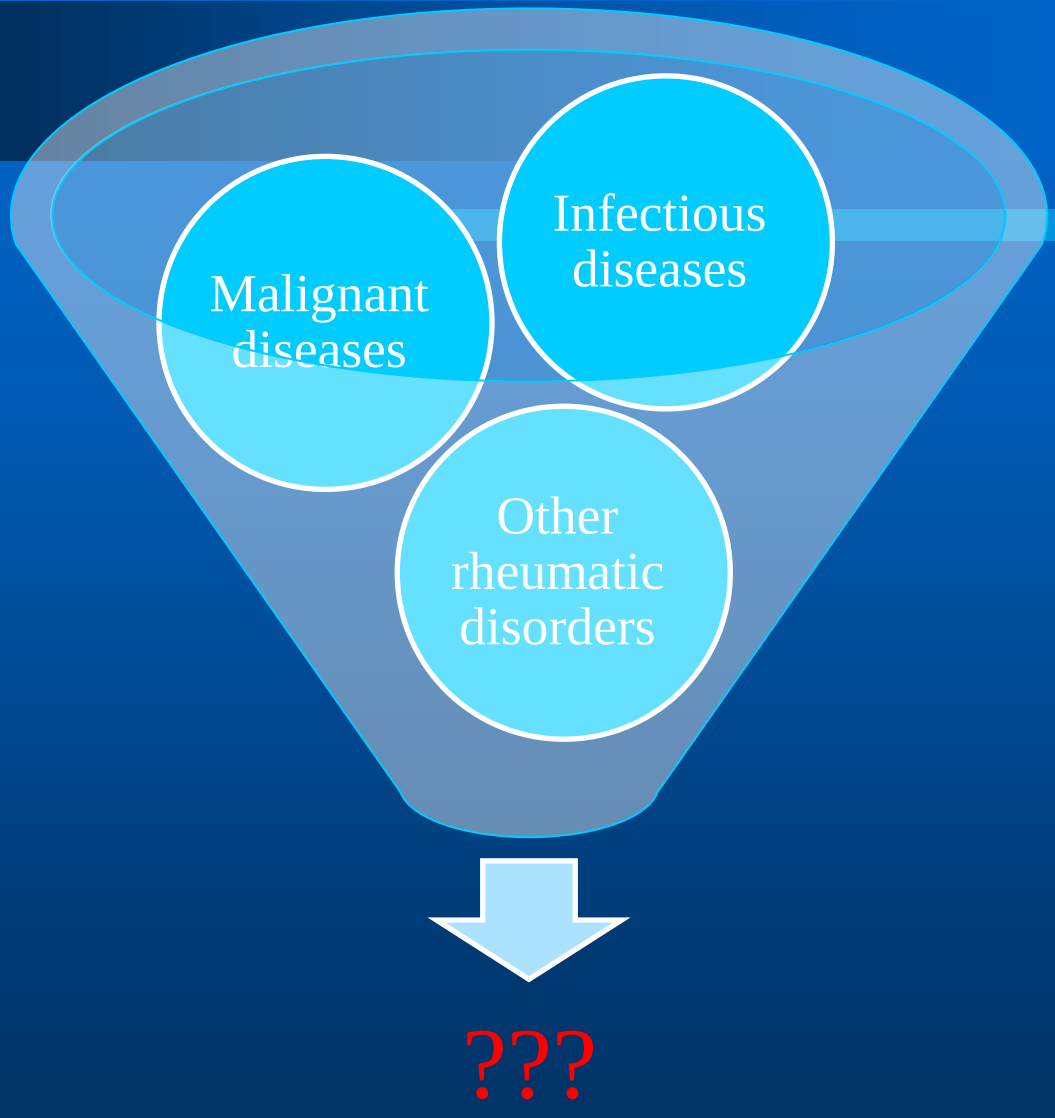
Laboratory tests

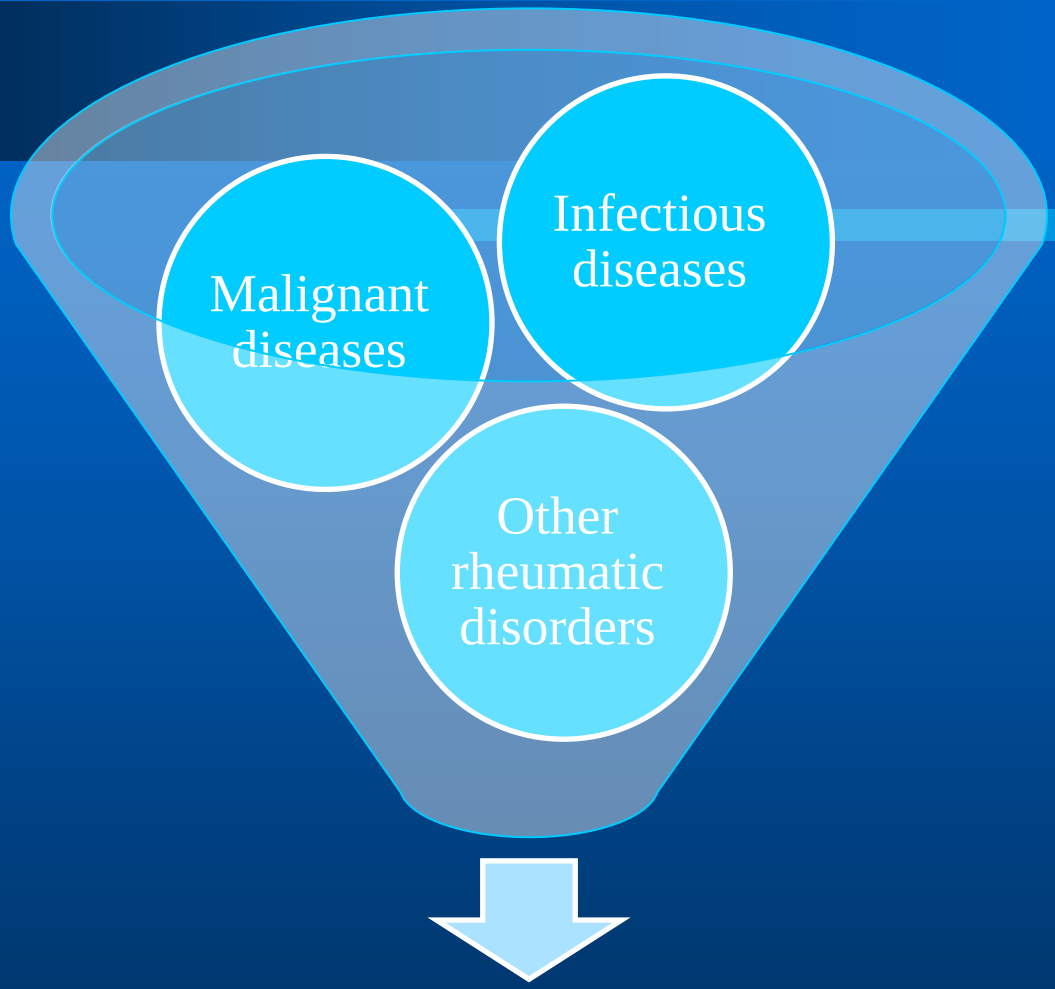
LDH (u/L) 60-225	↑ 240
Total Bilirubin (mg/dl) 0.2-1	0.9
Direct Bilirubin (mg/dl) 0-0.2	0.4
INR 0.75-1.3	1

ANA	-
RF	-
ACPA	–
ANCA	–

Laboratory tests

- Blood, urine and throat cultures were sterile.
- Serological assays for Epstein-Barr virus, Cytomegalovirus, Human immunodeficiency virus, Syphilis, Rickettsia, Q Fever, West Nile Virus, Parvovirus were negative.
- Protein electrophoresis, immune-electrophoresis and complement levels were normal. Urine analysis did not reveal red blood cells or protein.
- Chest radiography was normal.
- Computed tomography imaging of the thorax, abdomen and pelvis showed mild hepato-splenomegaly without lymphadenopathy or any sign of solid tumor.


Malignant diseases
Infectious diseases
Other rheumatic disorders
???



Adult onset still's disease

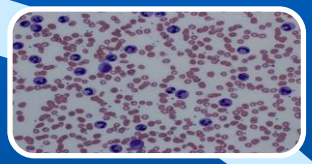
Yamaguchi criteria

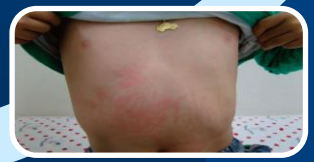
Diagnosis of AOSD requires ≥ 5 criteria including ≥ 2 major criteria

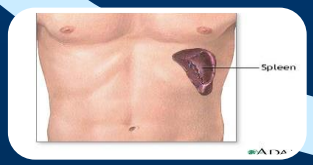
Major Criteria
Fever of at least 39.0 °C (102.2 °F) lasting at least 1 week
Arthralgias or arthritis lasting at least 2 weeks
A salmon-colored nonpruritic macular or maculopapular rash usually found over the trunk or extremities during febrile episodes
Leukocytosis (leukocyte count ≥10,000/μL [10×10^9/L]) with at least 80% granulocytes
Minor Criteria
Sore throat
Lymphadenopathy
Hepatomegaly or splenomegaly
Abnormal liver chemistry studies, particularly elevations in aspartate and alanine aminotransferase and lactate dehydrogenase levels
Negative results on rheumatoid factor and antinuclear antibody assays

Diagnosis

ANA, RF negative







AOSD

Treatment

- Intravenous methylprednisolone 100 mg/day was started with rapid resolution of fever, arthritis, rash and improvement in inflammatory markers and liver enzymes.
- The patient was discharged with prednisone 0.5 mg/kg/day for two weeks and recommendation to reduce the dose gradually.
- On discharge, ferritin 5000 ng/ml (on admission 3481 ng/ml), CRP 80 ng/L (on admission 225 ng/L), ALT 85 u/L, GGT 112 u/L.

2 weeks later

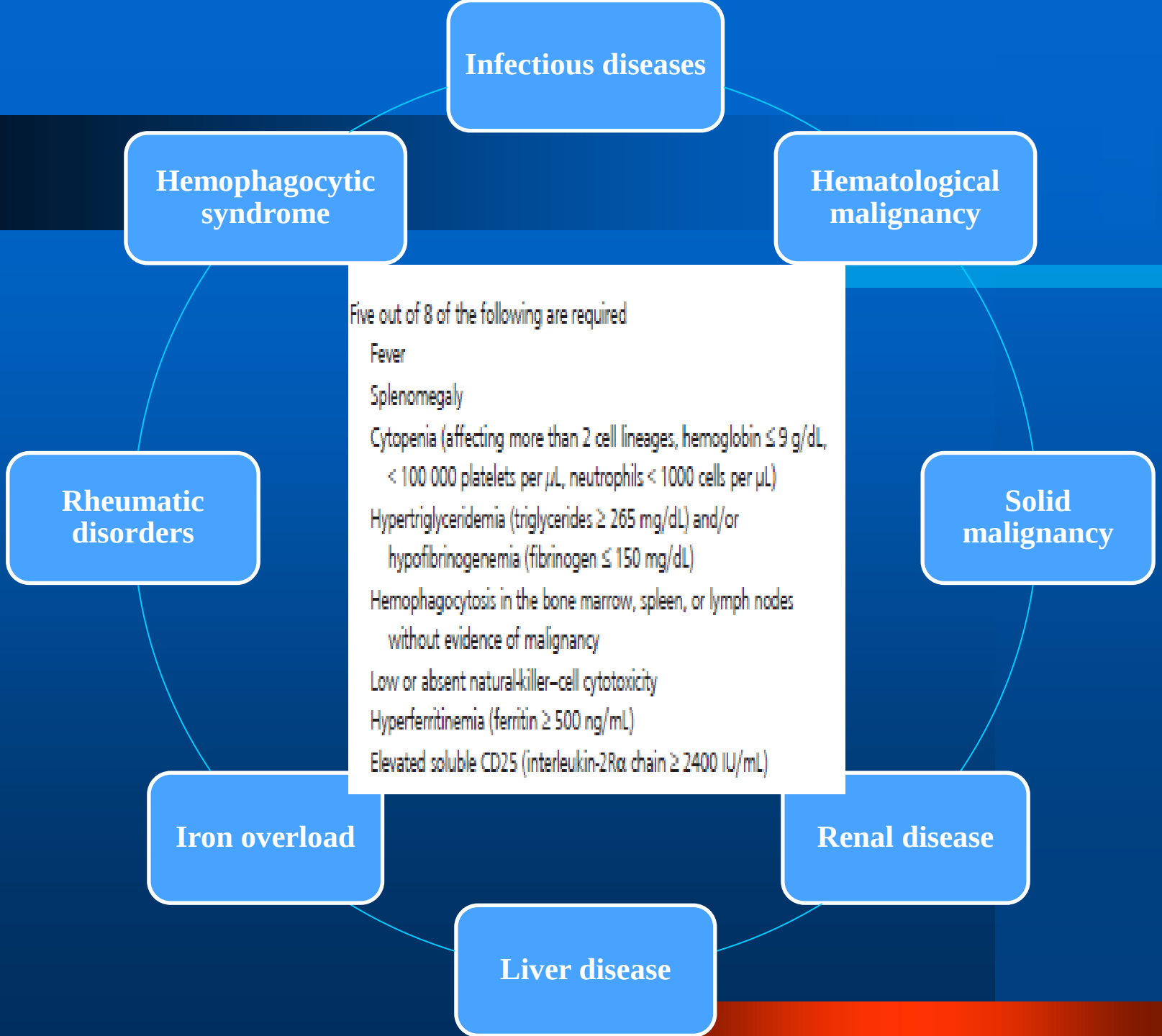
- While been treated with prednisone 40 mg/day, the patient complained of mild weakness.
- There was no fever, rash or arthritis.
- Physical examination was normal.

Laboratory tests

Ferritin (ng/ml) 15-300	↑ 12866
CRP (ng/L) 0-5	↑ 32

Albumin (g/dl) 3.5-5	↓ 2.8
AST (u/L) 5-40	↑ 48
ALT (u/L) 30-65	↑ 108
GGT (u/L) 5-60	↑ 96
ALP (u/L) 30-115	75

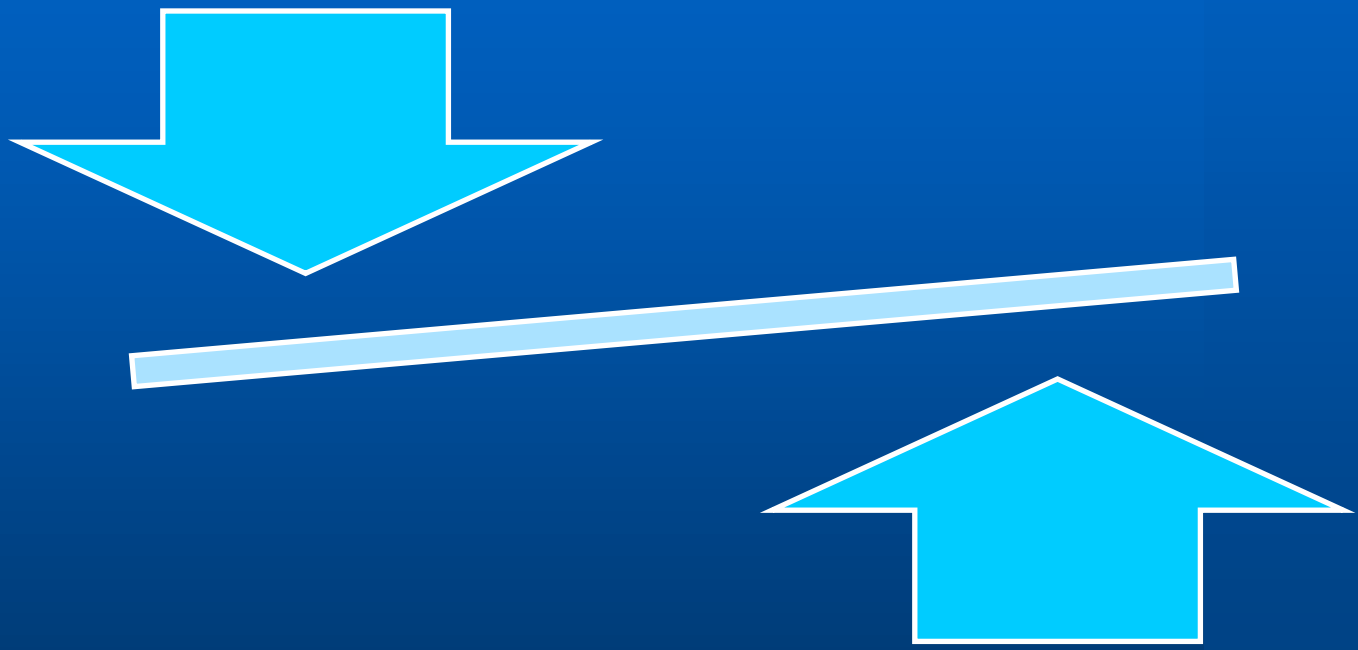
- Does the patient have still’s disease?
- Does the patient have a complication of still’s disease?
- Does the patient have other diagnosis?


Infectious diseases
Hematological malignancy
Solid malignancy
Renal disease
Liver disease
Iron overload
Rheumatic disorders
Hemophagocytic syndrome
Five out of 8 of the following are required
Fever
Splenomegaly
Cytopenia (affecting more than 2 cell lineages, hemoglobin ≤ 9 g/dL, < 100 000 platelets per μL, neutrophils < 1000 cells per μL)
Hypertriglyceridemia (triglycerides ≥ 265 mg/dL) and/or hypofibrinogenemia (fibrinogen ≤ 150 mg/dL)
Hemophagocytosis in the bone marrow, spleen, or lymph nodes without evidence of malignancy
Low or absent natural-killer–cell cytotoxicity
Hyperferritinemia (ferritin ≥ 500 ng/mL)
Elevated soluble CD25 (interleukin-2Rα chain ≥ 2400 IU/mL)

Hyperferritinemia

- Elevated serum ferritin levels is a typical finding in AOSD patients.
- Whether the elevated ferritin in AOSD has a pathogenic mechanism or is merely a by product of inflammation remains unknown.
- High ferritin levels can be present in a variety of inflammatory conditions. However in these conditions, serum ferritin concentrations rarely exceed values of > 3000 ug/L.
- Levels > 10000 ug/L has only been described in AOSD patients with severe liver damage, after multiple blood transfusions or in the hemophagocytic syndrome (HPS).

Treatment



The patient was recommended to reduce gradually the prednisone dose

One month later

- While been treated with prednisone 20 mg/day , the patient was readmitted because of severe hepatitis.
- He had no fever, vomiting, abdominal pain, arthralgia or rash.
- On physical examination he was alert, without jaundice or any stigmata of chronic liver disease.

Laboratory tests

WBC (x 10^3 /uL) **4-10.8**	12.6
Hgb (gr/dl) **13-17**	15
PLT (x 10^3 /uL) **130-350**	177

Creatinine (mg/dl) **0.2-1.3**	0.73
Ferritin (ng/ml) **15-300**	↑ 2562
ESR (mm/hr) **0-10**	10
CRP (ng/L) **0-5**	↑ 23.15

Albumin (g/dl) **3.5-5**	↓ 2.9
AST (u/L) **5-40**	↑ 788
ALT (u/L) **30-65**	↑ 3073
GGT (u/L) **5-60**	↑ 305
ALP (u/L) **30-115**	95

Laboratory tests

LDH (u/L) 60-225	441 ↑
Total Bilirubin (mg/dl) 0.2-1	2.7 ↑
Direct Bilirubin (mg/dl) 0-0.2	1.4 ↑
INR 0.75-1.3	1.4 ↑

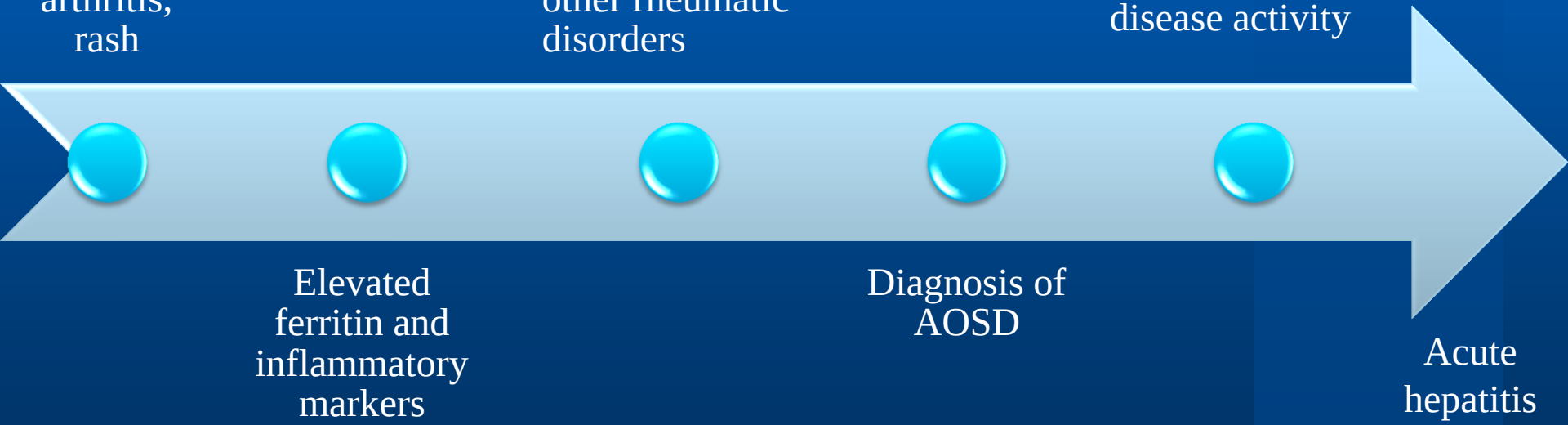
ANA	-
RF	-
ACPA	–
ANCA	–

- Tests were negative for:
  - HBV surface antigen
  - anti-HBcore IgM
  - anti-hepatitis A virus IgM
  - anti-HCV antibody
  - anti-CMV IgM
  - anti EBV IgM

Laboratory tests

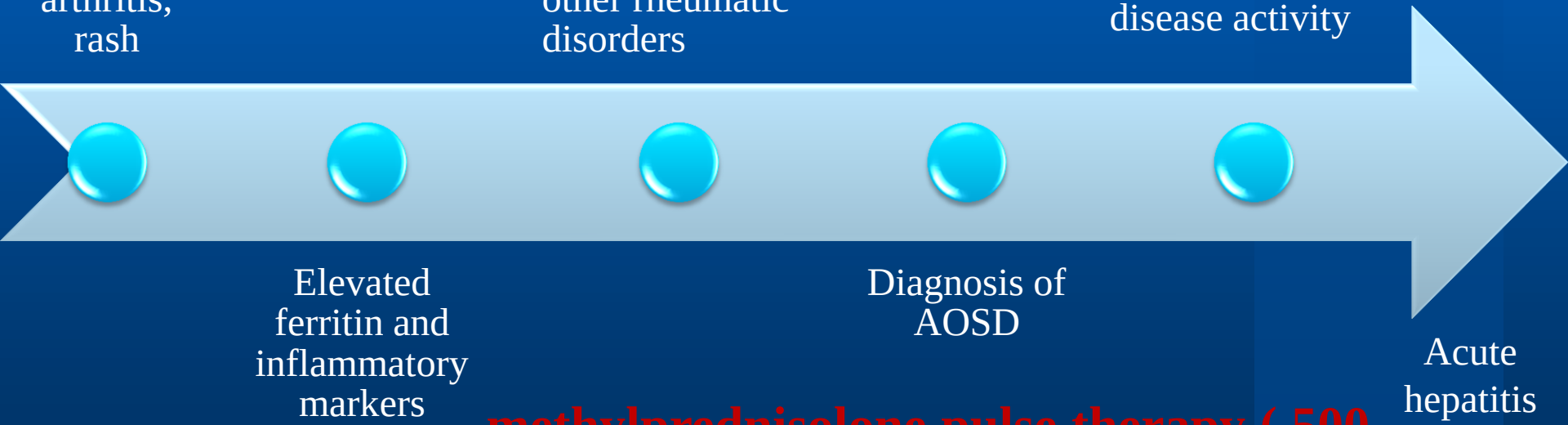
- Lactic acid level was normal.
- Acetaminophen was not detected in blood.
- Urine tests for toxins were negative.
- Anti smooth muscle antibodies, anti mitochondrial antibodies were negative.
- Serum ceruloplasmin level and immunoglobulins including IgG4 were normal.
- Abdominal ultrasound showed mild splenomegaly, with no sign of portal hypertension or thrombosis.

Summary



TREATMENT??

Summary



methylprednisolone pulse therapy (500 mg/day for three consecutive days) was administrated.

- Does the patient have still’s disease?
- Does the patient have a complication of still’s disease?
- Does the patient have other diagnosis?

Viral infections

- EBV, CMV and Parvovirus
- Reactivation of hepatitis B virus infection due immunosuppression

Medications

Autoimmune hepatitis

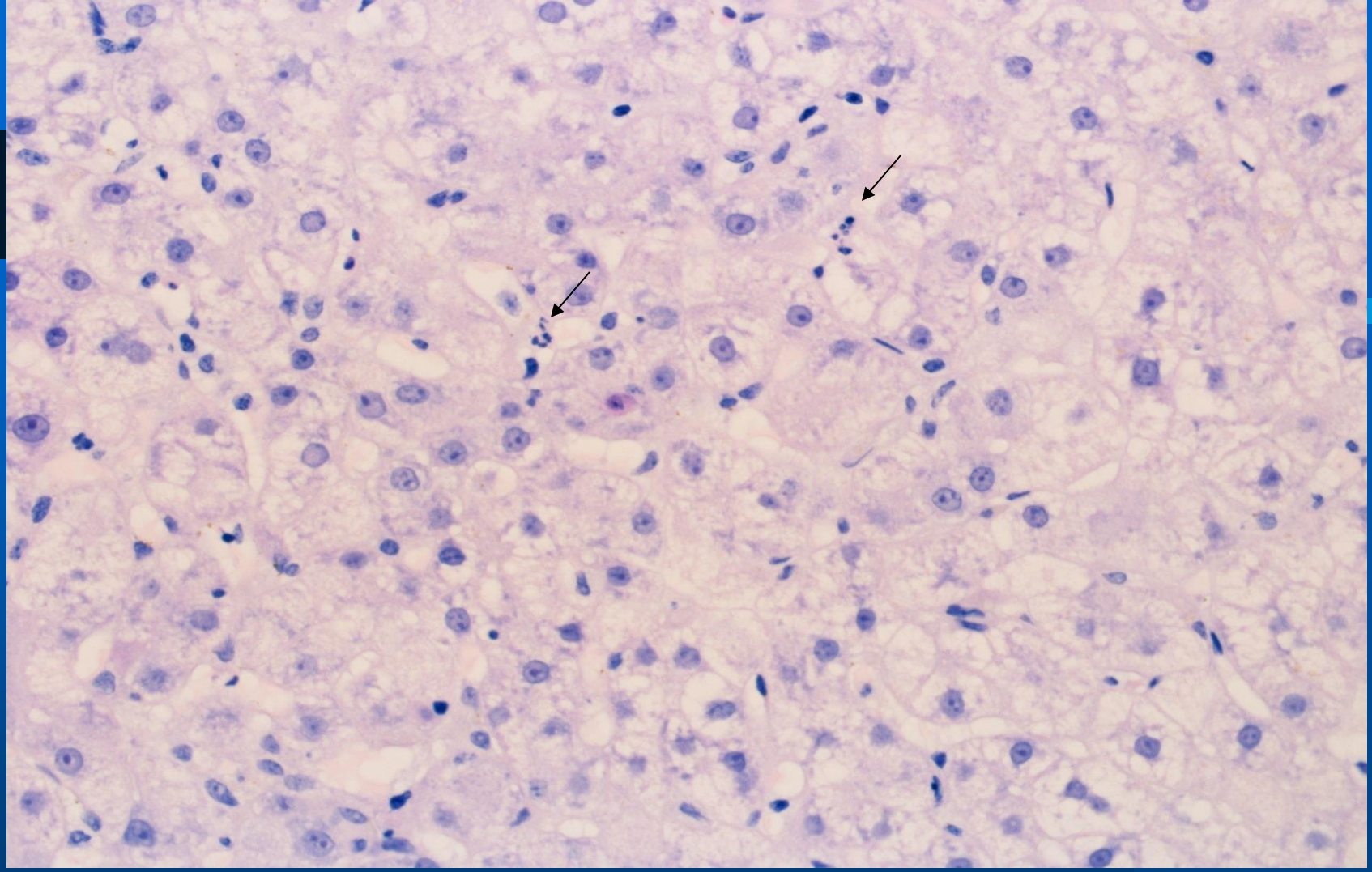
- AOSD patients + AIH have positive ANA in up to 10 % with marked hypergammaglubolinemia

Lymphoma

- Primary hepatic lymphoma

HSP

- HPS is reported in up to 12 % of AOSD cases
- Characterized by hyperpyrexia, hepato-splenomegaly, cytopenias, high ferritin levels
- It is often resistant to treatment and can be rarely a life-threatening complication



Acute unspecific reactive hepatitis with inflammatory cells infiltration, rich in neutrophils, occasional eosinophilic apoptotic bodies, hepatocytes with ballooning of the cytoplasm.

There were no signs of lymphoma, autoimmune hepatitis, or hemophagocytosis

Liver involvement in AOSD

- Liver involvement is common in Still's disease with a wide spectrum of abnormalities .

- Elevated liver enzymes can range from mild elevation to fulminant liver failure, rarely it is fatal and requires liver transplantation.

- There are only 17 reported cases of severe hepatitis in association with AOSD in the English literature. Five of the patients underwent liver transplantation; one patient developed encephalopathy, cardiac arrest and died.

Auther reference	Age/sex	Disease duration	Drugs before LF	Laboratory tests	Liver biopsy	Treatment of LF	Follow up
Takami et al 1995 [40]	74 / F	Simultaneously	-	ESR:75, CRP:10.1 AST/ALT:435/404 T Bil:0.63, Ferritin:1794.5	Y	Prednisolone PO	NA
Mcfarlane et al 1996 [41]	21/M	3 months	Acetaminophen Codeine	INR:26.5 AST/ALT:2710/2940 T Bil:27.6 Ferritin:18632	Y	IV pulse MTP then prednisone PO	Liver transplant acute rejection treated with OKT 3
Dino et al 1996 [42]	44/F	2 months	Aspirin	PT:16% AST/ALT:2370/1690 T Bil:47.8, Ferritin:930	N (PST)	IV pulse MTP	Liver transplant DIC, ARF death
Assy et al 2011 [43]	34/F	Simultaneously	-	ESR:100, INR 1.2 AST/ALT: 437/315 T Bil:0.6 Ferritin:30.000	Y	Prednisone PO	NA
Yamanaka et al 2003 [39]	20/F	3 years	Prednisone 15mg/d, CSA stopped	PT: 33 % AST/ALT:3052/3 T Bil:17.8	N (PST)	IV pulse MTP + Plasma pheresis	Liver transplant Prednisone + Tacrolimus
Omagari et al 2003 [44]	48/F	Simultaneously	-	ESR:13, INR:22 sec AST/ALT:972/711 T Bil:7.8, Ferritin:32240	Y	IV pulse MTP Prednisone + CYS	drugs tapered over 5 months
Ott et al 2003 [45]	25/F	2 years	prednisone 16 mg/d	ESR:56, PT: 65 % AST/ALT:528/1067 T Bil:28.1, Ferritin: 1189	Y	Prednisone PO + UDCA	2 years Prednisone 5 mg/d

Auther reference	Age/sex	Disease duration	Drugs before LF	Laboratory tests	Liver biopsy	Treatment of LF	Follow up
Ogata et al 2003 [46]	20/F	3 years	Prednisone 15mg/d, CSA stopped	CRP:13 AST/ALT:2040/3990 Ferritin 583.1	N (PST)	IV pulse MTP Plasma exchange	Liver transplant acute rejection Prednisone+FK506
Mylona et al 2007 [47]	46/M	2 months	Prednisone taper	CRP:1.13, PT: N AST/ALT:685/3009 T Bil:1.5, Ferritin:2768	Y	Prednisone SC Anakinra 100 mg/d	5 months Prednisone taper + Anakinra
Taccone et al 2008 [9]	28/F	1 month	Prednisone 8 mg/d	PT: 9 % AST/ALT:2186/1148 T Bil:33,Ferritin:27132	N (PST)	IV pulse MTP MARS	Liver transplant 1 year Prednisone+Tacrolimus
Thabah et al 2008 [48]	29/F	< 1 month	Prednisone 40 mg/d	ESR:90, PT:28sec AST/ALT:4180/- 2210 T Bil:4.7, Ferritin:6364	N (PSM)	Prednisone	Died
Nagashima et al 2008 [49]	51/F	3 years	Prednisone 5mg/d, MTX 6mg/week	CRP:1.33, INR:N AST/ALT:1556/2329 T Bil:9.8, Ferritin:17700	Y	IV pulse Dexa. CSA 3mg/kg (120mg/d)	2 years Prednisolone 8 mg/d
Nagashima et al 2008 [49]	32/F	Simultaneously	-	CRP:0.55 AST/ALT:344/1260 Ferritin:5167	N	IV pulse Dexa. CSA 3mg/kg (150mg/d)	1 year Prednisolone 4 mg/d
Feng Yeh et al 2009 [50]	27 M	2 years	Prednisolone 10mg/d,MTX 10mg/week	ESR:4, PT:14.3sec AST/ALT:955/1081 T Bil:16.5, Ferritin:21643	N	IV MTP CSA 2.5mg/kg (150mg/d)	2 months Prednisolone 45mg/d+CSA

Auther reference	Age/sex	Disease duration	Drugs before LF	Laboratory tests	Liver biopsy	Treatment of LF	Follow up
Hogan et al 2011 [51]	35/F	3 months	Sulfasalazine	INR:2.9 AST/ALT:1908/1148 T Bil:4.7, Ferritin 31425	Y	IV MTP Prednisone taper	NA
Singh et al 2013 [24]	29/F	1 month	-	INR:3.5 AST/ALT:2736/1738 T Bil:5.2	Y	IV pulse MTP IV Infliximab 5mg/kg -8weeks	NA
Harmanci et al 2013 [52]	34/F	2 months	-	ESR:79, INR:4.3 AST/ALT:1470/530 T Bil:9.3, Ferritin: 11600	Y	Prednisone 1mg/kg IVIG 30gr/week	NA

- Liver dysfunction may occur simultaneously at the time of AOSD diagnosis, during the steroid taper or many years after remission.
- It affects women slightly more frequently than men.
- The disease onset is usually between 20-35 years.

Pathophysiology

- The precise mechanism of liver dysfunction associated with AOSD is unclear.
- IL 18 is though to mediate the hepatotoxic manifestations of AOSD.
- Circulating IL 18 is markedly increased in patients with fulminant hepatic failure compared to those with chronic liver disease.
- Activated macrophage and kupffer cells within the liver parenchema overexpress locally IL 18.
- IL 18 levels have been found to correlate significantly with serum aminothransferase levels.

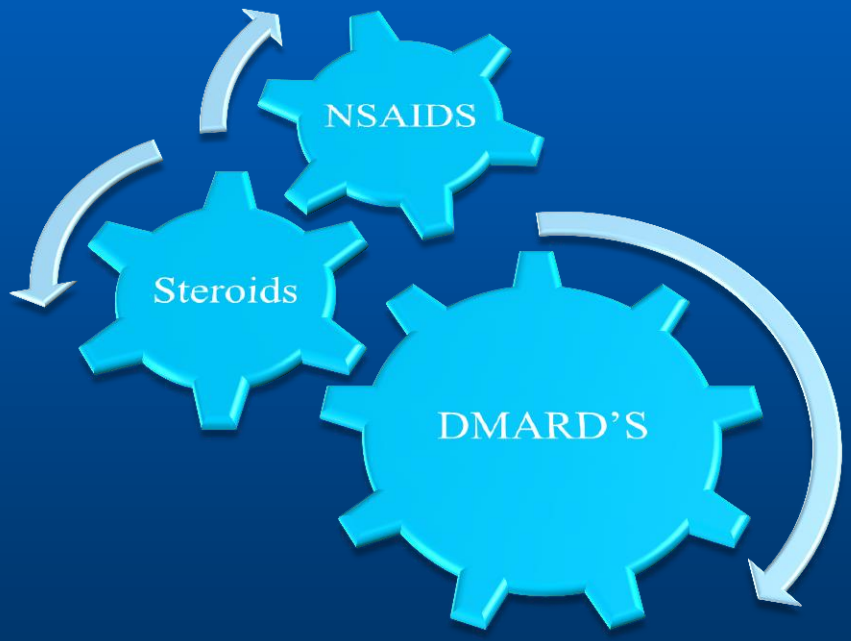
Summary

- Our patient had still's disease and was complicated with severe elevation of liver enzymes.
- After exclusion of various causes of liver impairment, hepatitis was attributed to AOSD itself.
- Markedly high levels of ferritin preceded the development of acute severe hepatitis.
- In this case, elevated ferritin was the only marker of disease activity.
- Elevated ferritin levels > 10000 in AOSD patient's should point to development of hepatic failure or HSP.

Liver biopsy

- The role of liver biopsy for establishing the diagnosis of AOSD is limited, but it has important role in revealing other causes of liver failure which can influence the therapy and outcome of the patient.

Treatment



Methotrexate
Azathioprine
Cyclosporine A
Leflunomide

IVIG

Cyclophosphamide

As our understanding of the role of cytokines in AOSD pathogenesis has expanded, the management of severe cases has included biologic agents targeting pro-inflammatory cytokines.

Rilonacept

(an IL1 trap molecule that is soluble dimeric fusion protein)

Canakinumab

(anti IL 1 β monoclonal antibody)

Anakinra

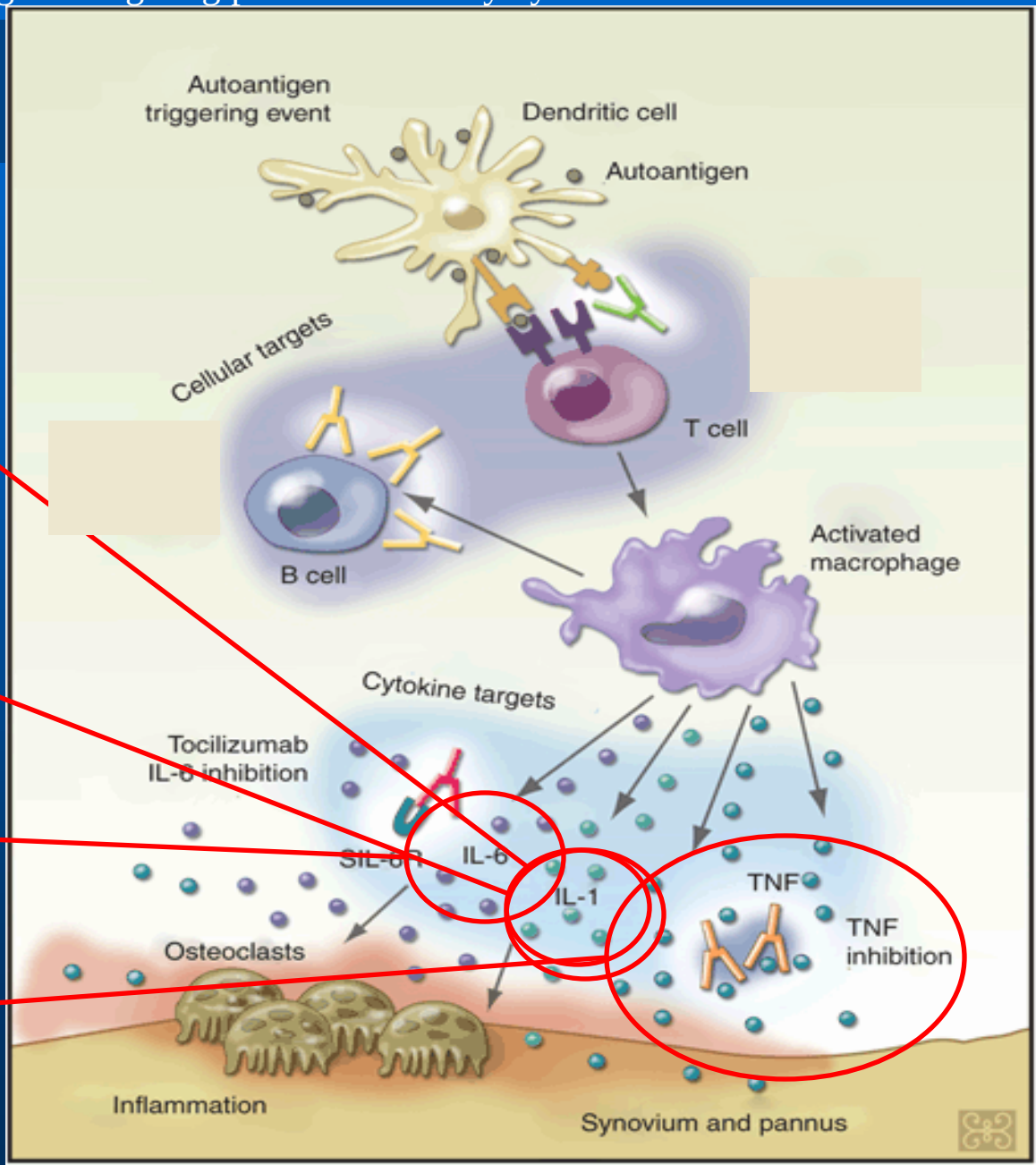
(recombinant IL 1 receptor antagonist)

Tocilizumab

(IL 6 receptor monoclonal antibody)

Anti TNF agents :

Infliximab , Adalimumab , Etanercept



Treatment of AOSD with liver dysfunction

- Treatment of severe liver impairment in patients with still’s disease is challenging and mainly is aimed to treat AOSD itself.
- The liver dysfunction is supposed to resolve rapidly with steroid treatment.
- In the present case, severe hepatitis developed despite steroid treatment, therefore it was necessary to start second line treatment.
- The elevated liver enzymes made the choice difficult because most of the DMARD'S can cause liver toxicity.

- MTX can induce steatosis, hepatic fibrosis and liver toxicity.
- Azathioprine is associated with nodular hyperplasia and deranged liver enzyme levels.
- Hydroxychloroquine and leflunomide have both been reported to cause severe hepatitis and liver failure.
- Anti TNF agents, Tocilizumab and Anakinra have also been reported to induce acute hepatitis.

I love days

when my only

problem is ...

or

tea

coffee

- CSA has been reported to be effective in some cases with AOSD complicated with severe hepatitis and HPS.
- CSA is a calcineurin inhibitor that targets T cells and prevents cytokine production.
- IV methylprednisolone pulse therapy (500 mg/day for three consecutive days) was administrated with Cyclosporine A (CSA) 100 mg/day.
- A few days later, the liver enzymes improved, and the levels of bilirubin and INR normalized.

- The patient was discharged with recommendation to continue CSA 150 mg/day and prednisone 60 mg/day.

- During his follow up examination, there was rapid normalization of liver enzymes within the next three weeks. This effect was sustained during his follow-up despite the reduction in prednisone dose (10 mg/day).

- It is unknown whether the disease can remain in remission with no or minimal treatment.
- In our patient close follow up is mandated to monitor any disease activity.
- The long term maintenance dose and the length of CSA treatment should be estimated carefully.

Conclusions

- Markedly elevated serum ferritin levels could be the only manifestation of AOSD activity and could precede hepatic impairment.
- Therefore, monitoring of ferritin levels and liver enzymes is recommended.
- Treatment of severe liver impairment in the context of AOSD is challenging and mainly is aimed to treat AOSD.
- Most of the DMARD'S can cause liver toxicity.
- Prompt initiation of CSA can improve liver function and prevent progression to liver failure.