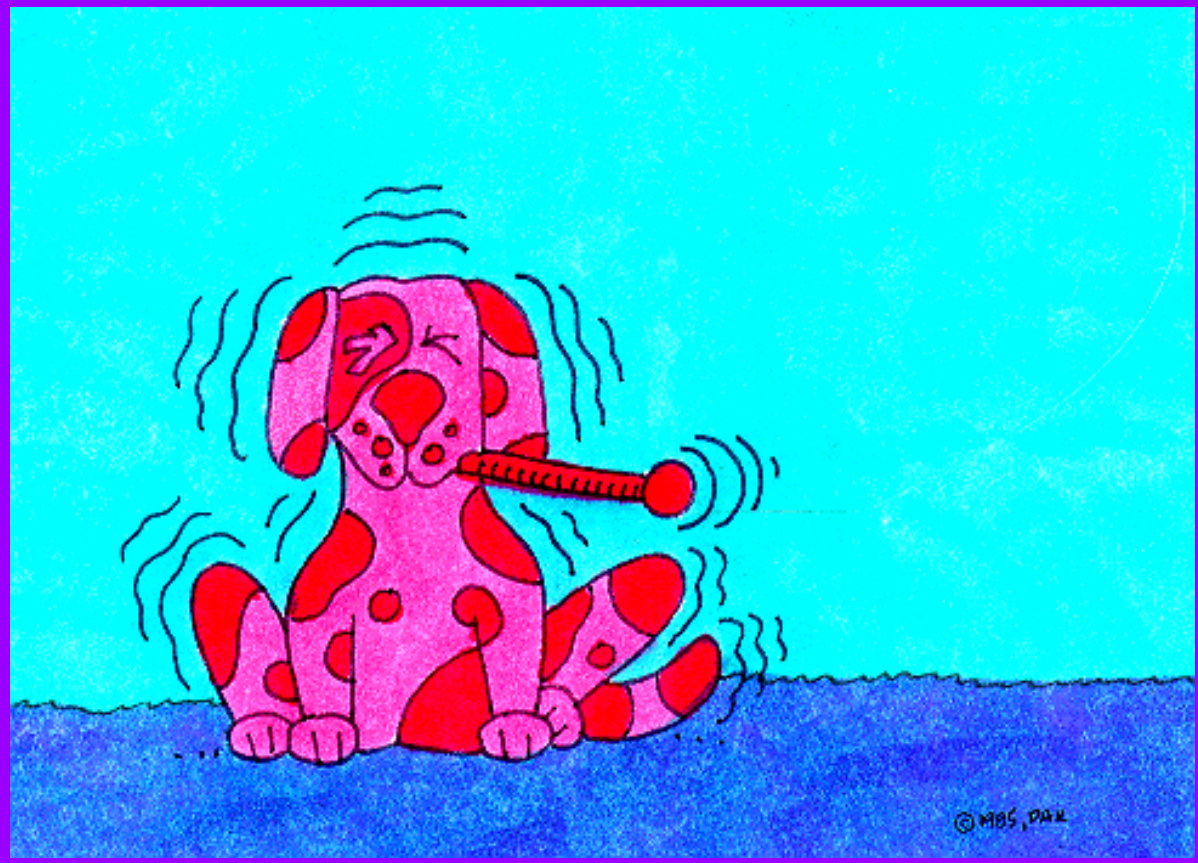

Autoinflammatory syndromes and periodic fewers

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Autoinflammatory syndromes

Clinical entities chracterized by repeated attacks of fever without apparent infectious or autoimmune origin

Several clear define entities are members of this cathegory:

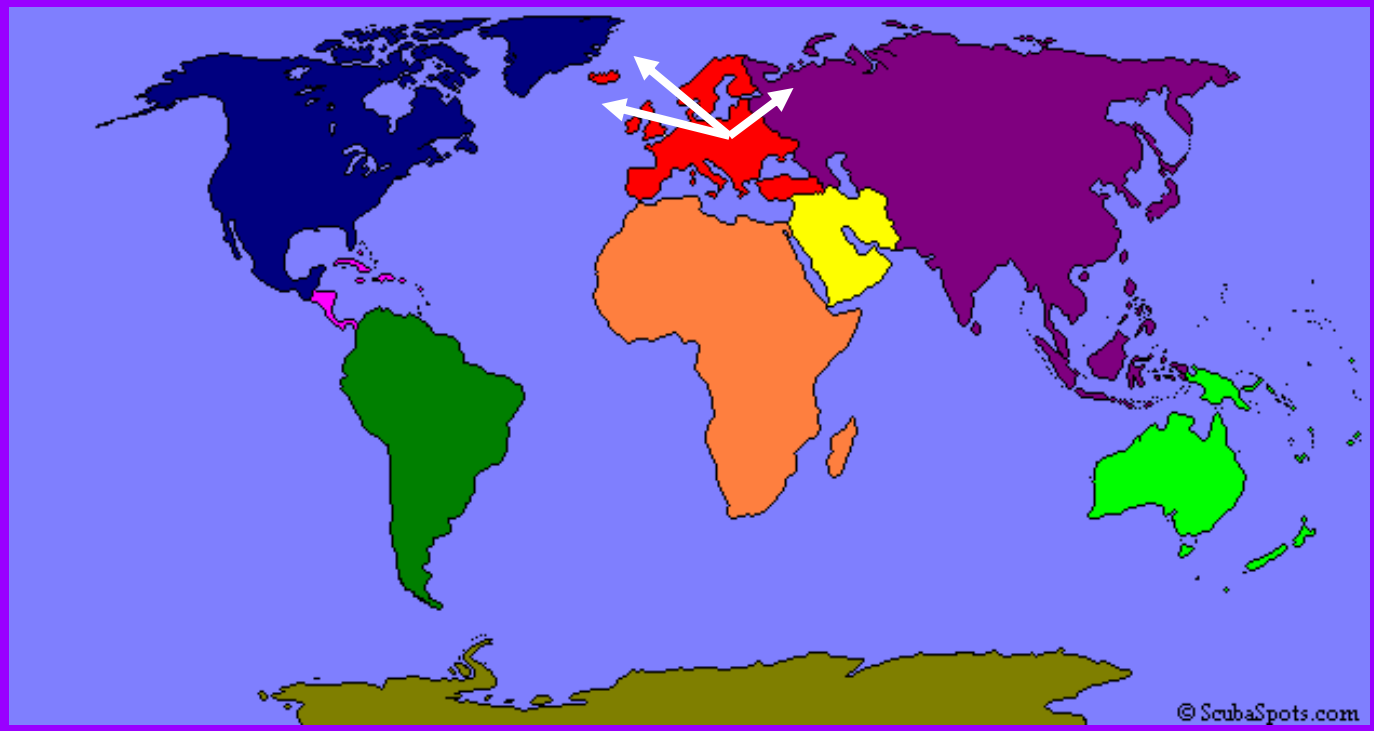
Familar Mediteranean Fever, FMF, caused by mutations in gene MEFV discovered in 1997 and protein pyrin described in 1999,
FCAS, „familiar cold autoinflammatory sydrome“, MWS, „Muckle Wells syndrome“ NOMID „neonatal onset multisystem inflammatory disease“ or CINCA „chronic infantile neurologic cutaneous and articular syndrome“ with common causative gene CIAS1 and protein cryopyrin
PAPA syndrom (sterile pyogenic arthritis, pyoderma gangrenosum and akne)
Blau syndrom and Crohn disease, caused by mutations in NOD2.
Hyper IgD syndrom is classical metabolic disease caused by mutations in mevalonate kinase and TRAPS syndrom by mutations in TNF receptor, TNFRSF1A.

„autoinflammatory syndromes“

disease		inheritance	chromosome	gene
Familiar Mediteranean fever	FMF	AR	16p13	*MEFV*
Mutation TNFRSF1	TRAPS	AD	12p13	*TNFRSF1*
Hyper IgD syndrome	HIDS	AR	12q24	*MVK*
Muckle-Wells synd.	MWS	AD	1q44	*CIAS1* *cryopyrin* *NALP3*
Familiar cold urticaria	FCU			
NOMID/CINCA	NOMID/ CINCA			
pyog.artritis,pyod. gangr.,acne	PAPA	AD	15q24	*PSTPIP1*
Blau syndrom		AD	16q12	*NOD2* *CARD15*

FMF

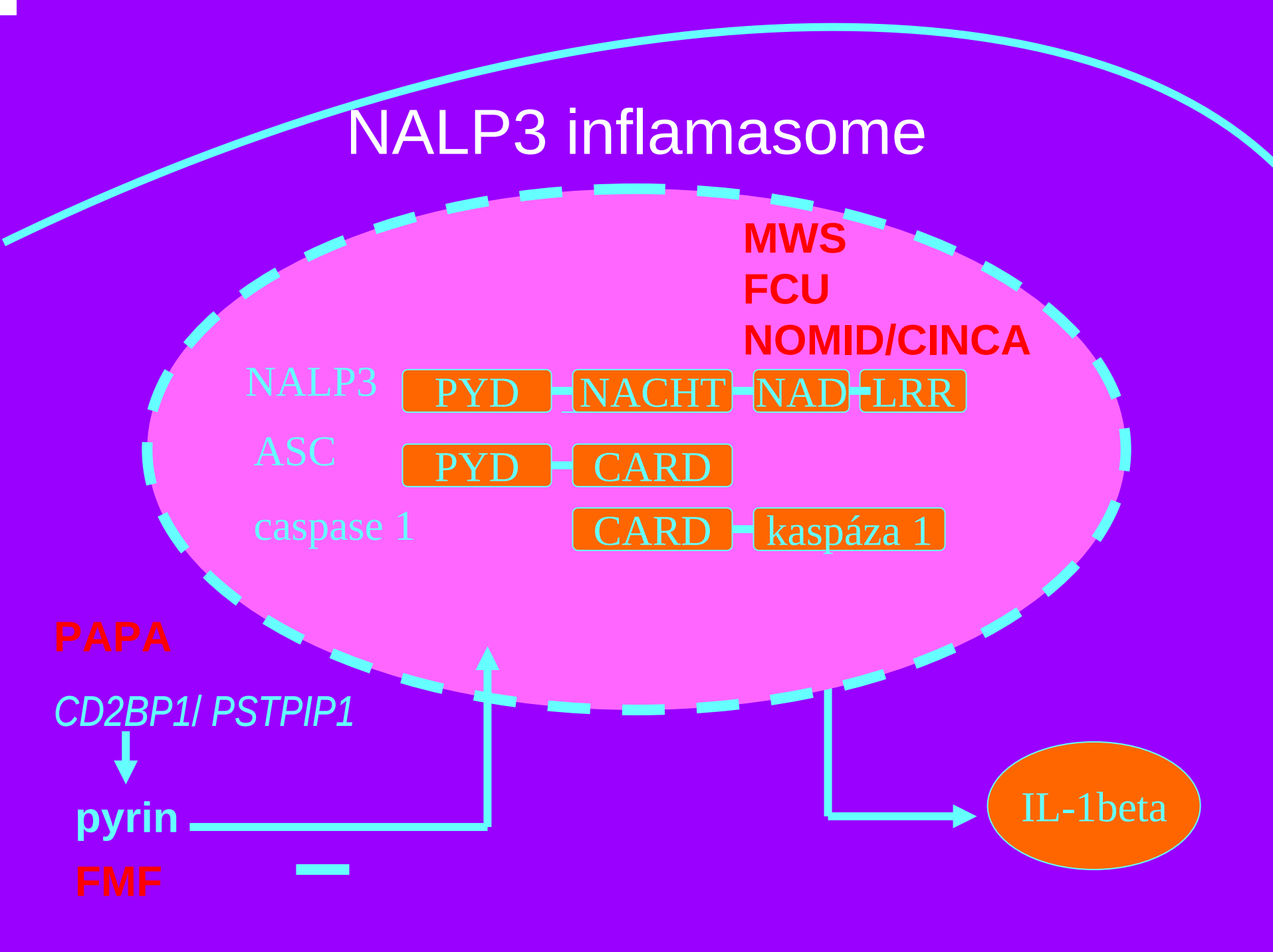
Common mutation with estimate of origine approximately 2500 years ago



MWS, FCU, NOMID/CINCA

- 1999 MWS, 2000 FCU, 2002 NOMID/CINCA
- gene 1q44, *CIAS1/NALP3/cryopyrin*
- cold induced autoinflammatory syndome
- NACHT,LRR and pyrin domain containing protein

NALP3 inflamasome



NOD2 complex

Familial Shar-Pei fever

Familial Shar-Pei fever is a periodic disease occurring in Shar-Pei dogs. Clinically, the disease resembles FMF: febrile attacks are accompanied by arthritis, peritonitis,
pleuritis, and amyloidosis. The MEFV gene is not found in the dog.

Case report

- Children – confirmed diagnosis hyper IgD syndrom
- Adults – unusual case of Schnitzler syndrome

The clinical riddle

peculiar or unresolved cases provided by ESIDJuniors

ESID newletter, case No 2

42 y-o man suffering from recurrent fevers and hives

The symptoms had relatively clear beginning in 2002. A few weeks before the first episode of severe fevers and exanthema the patient was heavily bitten by insect while visiting Spain. The first attack was accompanied with urinary tract infection (UTI) and prostatitis followed by gastrointestinal disturbance. Since then the frequency of attacks has increased, there have been only short asymptomatic intervals. Apart from intermittent febrile attacks and hives he complained of arthralgia without swelling of the surrounding tissue. Since beginning of the disease he has lost about 12 kg.

The clinical riddle
Investigation

The inflammation markers (erythrocytes sedimentation rate - ESR, C-reactive protein - CRP, number of leukocytes) has been permanently increased. There has been neutrophilia and lymphopenia, no eosinophilia. Level of IgG slightly above norm (16.20...11.20 g/l), IgM significantly high with tendency to increase (4.25...7.09 g/l), monoclonal gammapathy IgM kappa was found. Circulating immunocomplexes have been increased. ANA autoantibody showed mild positivity in 1:80 titre, other autoantibodies were negative. Antibodies against vaccination antigens were created, extended serology was insignificant, apart from high titre of IgG VCA EBV and CMV anamnestic antibodies. Investigation of cellular immunity did not show any abnormalities. Proliferation assay and chemiluminescence were normal. Serum chemistry was within normal limits, level of angiotensin-converting enzyme (ACE) was low. He has had repeated biopsy of bone marrow, there were no signs of malignancy. PET, CT gastroscopic and colonoscopic were investigation without pathological findings as well.

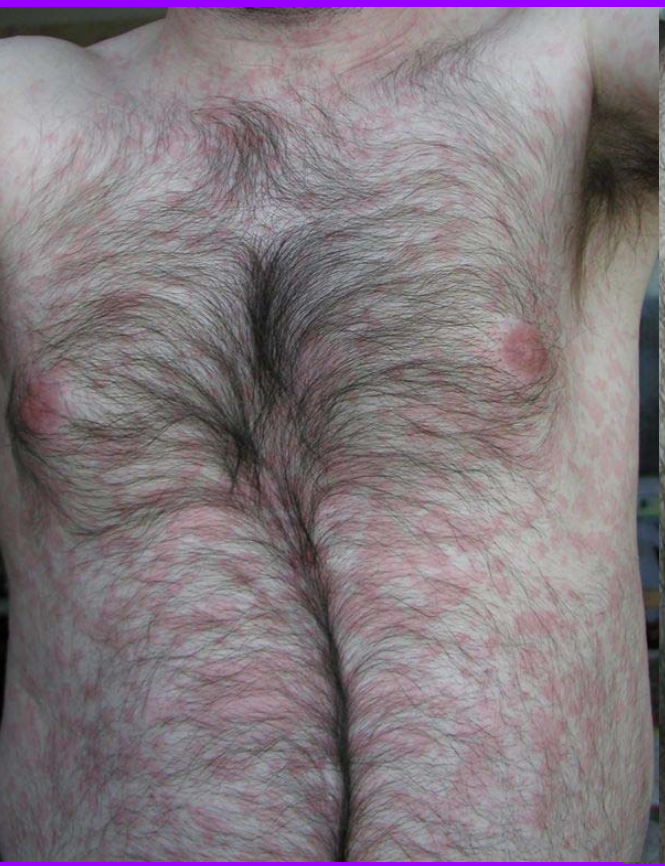
The clinical riddle
Therapy

He was treated with several antibiotics without any substantive effect. Use of steroids brought him relieve only for a few hours than the fevers relapsed. Non-steroidal anti-inflammatory drugs (NSAID) showed minimal effect as well as a trial with colchicin.

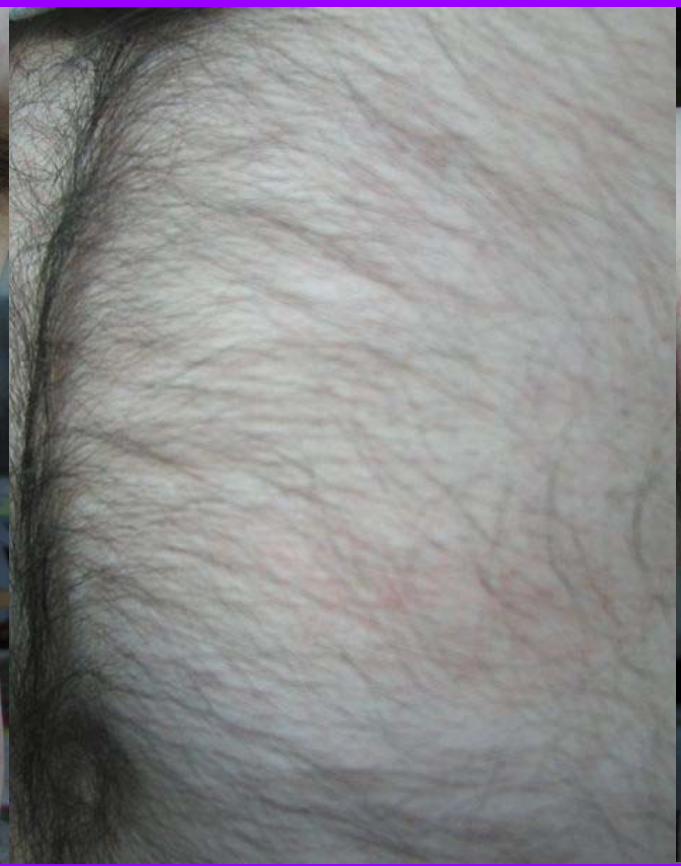
The clinical riddle
Therapy

Based on the clinical course of the disease we diagnosed him with one of the periodic fever syndromes - **Schnitzler syndrome**. In October 2006 we started daily anti-IL-1 therapy with Anakinra (Kineret). We saw an immediate effect of the therapy. However, due to the complicated funding of this extremely expensive drug, the patient has been transiently without the medication. Each time when the treatment was discontinued the symptoms occurred with increased severity. The only adverse reaction of Anakinra administration seen was mild erythema in the place of injection. Apart from the clinical improvement, the laboratory markers of inflammation substantially decreased, however we have detected progressive slow increase of IgM levels (currently approx. 7 g/l).

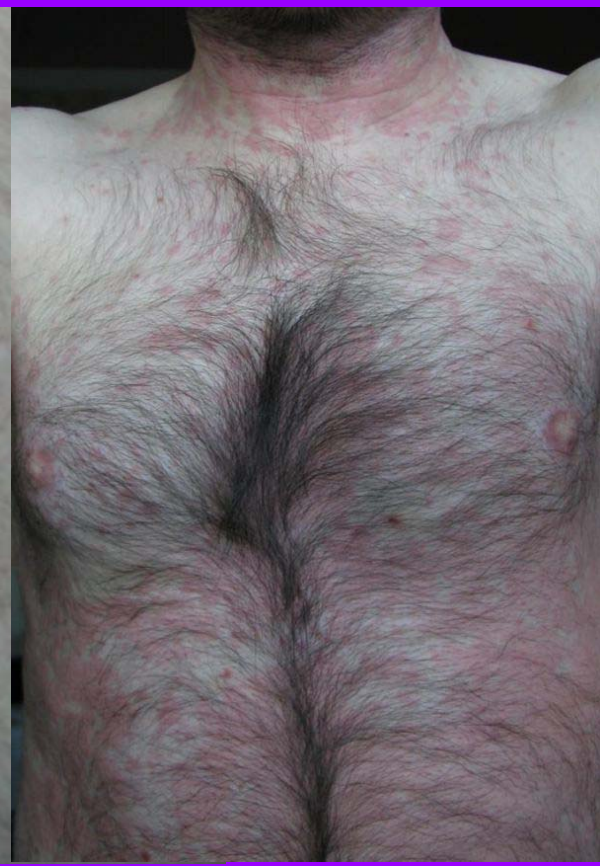
Case report
effect of therapy IL-1RA



before treatment

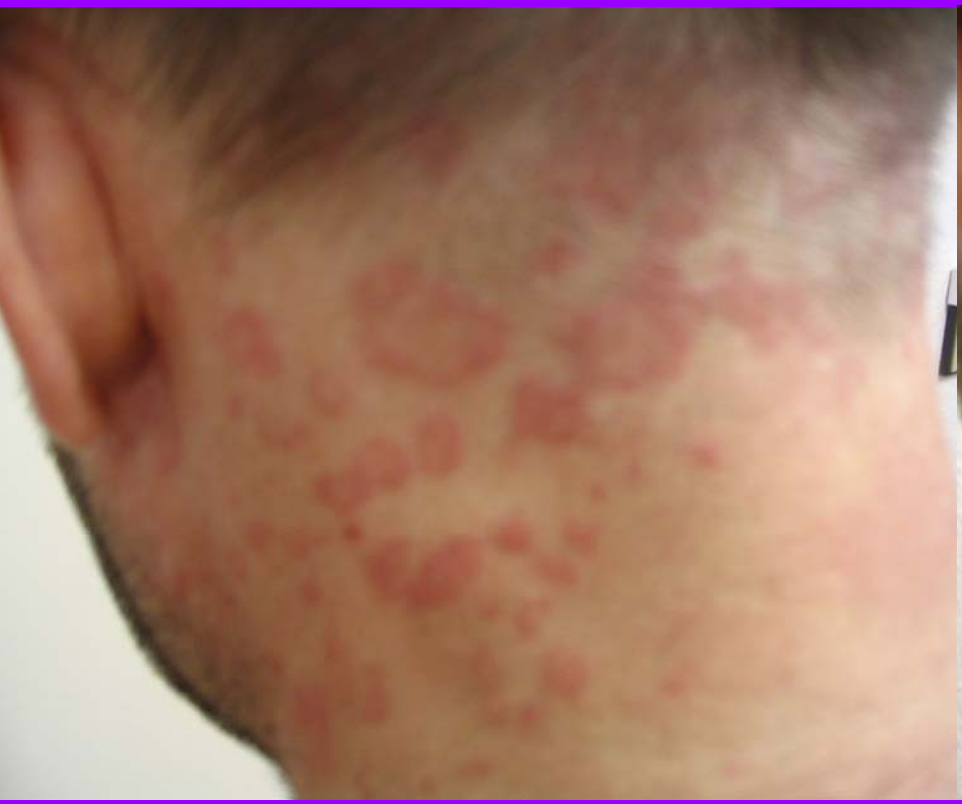


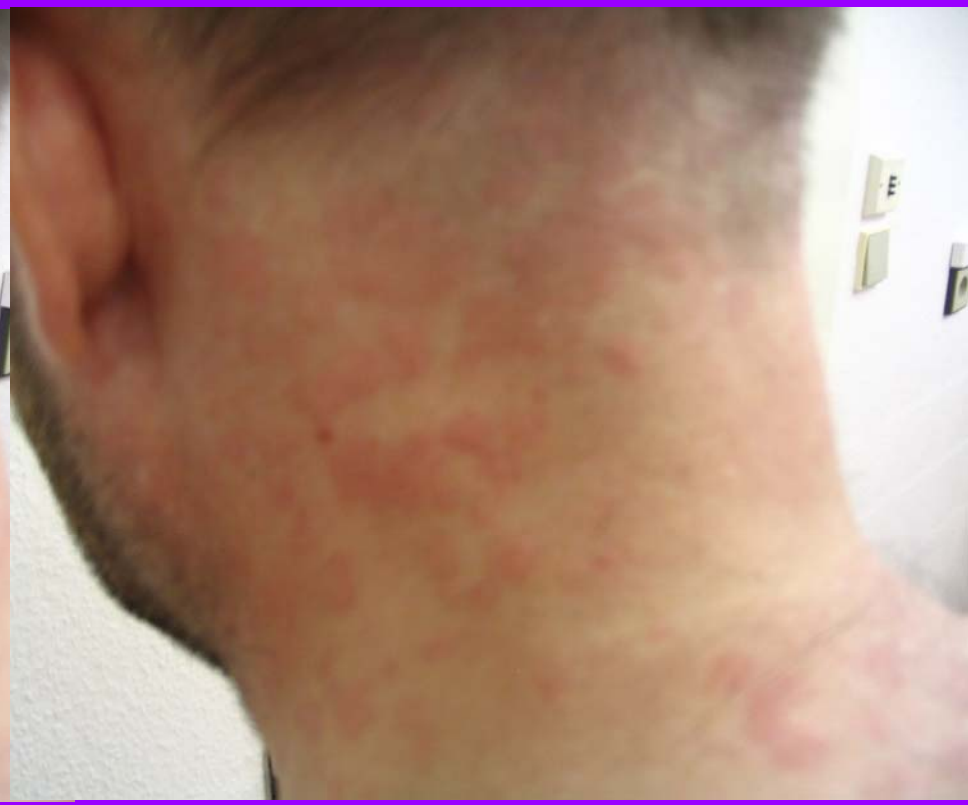
during treatment



after treatment

Case report
effect of therapy IL-1RA





Day of application 8.26 am

11.56 am

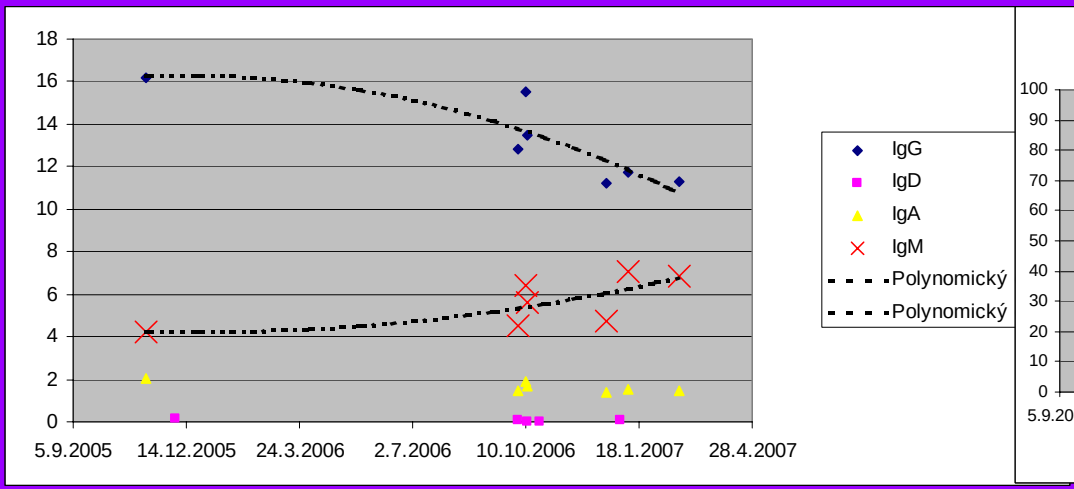
Case report laboratory

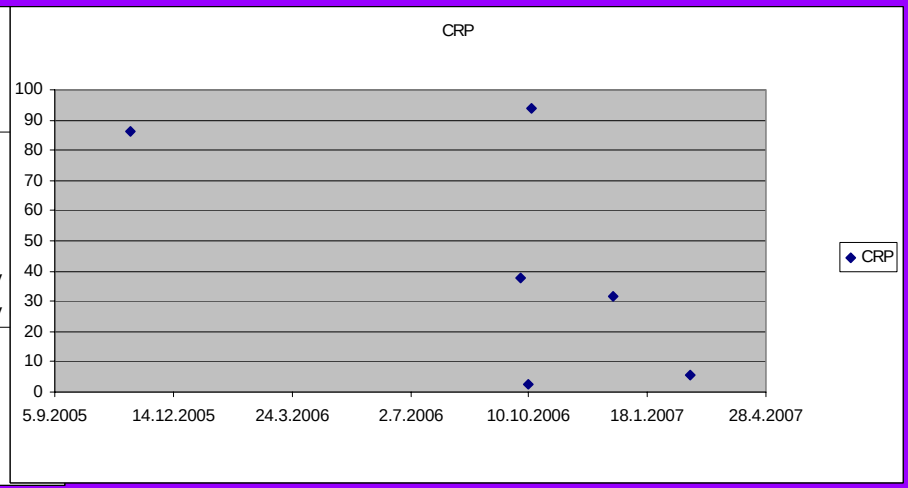
Sample	3.10.2006	10.10.2006	12.10.2006	parent	reference range (%)
lymfo,Freq. of Total	12,5				
CD3+	64,1				
CD3+CD8+	17,2				
CD3+CD4+	43,2				
CD19+	12,5	12,6	21,5	45+	4.7-15.0
IgD+CD27+ (IgM memory)	4,63	43,7	62,2	19+	7.8-36.0
IgD-CD27+ (switched,, memory B cells, plasmablasts)	2,98	3	2,8	19+	6.5-33.0
IgD+IgM++	2,98	4,28	3,6	19+	
IgD+IgM+ (naive and IgM memory)	26	66	77,2	19+	62.0-92.
IgD+IgM-	65,1	20	12,5	19+	
IgD-IgM- (switched B cells)	3,98	1,9	1,8	19+	7.7-36.0
CD19+CD27+ (memory B cells)	8,49	8,02	9	19+	

beginning of the treatment

increase of naive and IgM memory B cells

Case report laboratory





Open case

What is the long-term prognosis of these patients treated with Anakinra?
How to finance this extremely expensive therapy?
What is the danger of lymphoproliferative disorder or Waldenström macroglobulinaemia in this patient?
Is it reasonable to use anti-CD20 therapy?

ESID newsletter unusual case reports
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