Fever of unknown origin

Case B

-

- **History of the present illness**
- **75 years old women presented at our hospital with since months daily fevers between 38 to 39.5° Celsius (100.4°-103.1° F) with night sweats. Her complaints were of fatigue, dizziness and nausea. Besides the febrile episode she felt well. Attacks of fever occurred sometimes 2 times a day, some days she had 3 days following without fever. She lost 10 kilograms in 1 month. She had no recent tick bites or other infections. She was recent back from holiday in France. During holiday and before she had no contact with domestic animals, no tuberculosis contact, no erythematic rash, no photosensitivity, no Raynaud's phenomenon, no ulcers, no stiffness over the muscles of the legs and arms, no visual or hearing problems. No jaw claudication and no arthritis. There was no family history of autoimmune disease. She took no medications.**
-

- **Medical history**
- **Diabetes Mellitus type II, atrium flutter**
- **Medications and allergies**
- Atenolol/chloortalidon 1dd100/25 mg, Metformine 2dd500 mg

Physical examination and tests

- Physical examination revealed fully alert, oriented, and lucid sick women. Her vitals sign were as follows. Blood pressure 150/80 mm Hg, Heart beat 76/minute, her oxygen saturation was 95% on room air, and Temperature 37.8 ° Celsius (100° F), her respiratory rate was 18 breaths/minute unlabored. Unilateral right sided supraclaviculair lymphadenopathy with
- Right thyroid gland nodule. Examination of her heart revealed an irregular tachycardia (atrial flutter on ECG) but no murmurs, rubs, or gallops. The lungs were clear to auscultation. There was no evidence of hepatosplenomegaly, skin rash, focal motor weakness, sensory deficits or arthritis.

Laboratory examination

- elevated inflammation levels (CRP 133 mg/L, BSE 48 mm/h). Leucocytes 13.1/nL Neutrophils 11/nL ,
- Calcitonin lightly elevated. No M protein detectable, ACE not elevated. Assays for antinuclear antibodies, antibodies to double stranded DNA, rheumatoid factor, anti-neutrophil cytoplasmic antibodies, anti-phospholipid antibodies, and cryoglobulins were negative.
- The serum C3 and C4 levels were normal. A serum protein electrophoresis test showed normal levels of all immunoglobulin and no monoclonal spike.

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Bestand Bewerken Beeld Modules Venster Help

Document archief | Gegevens van patiënt 24040433... | Cumulatief Overzicht

Scally-Lelyveld, G.F.J. de — Geboren 10-02-1935 V

Patiëntnummer 24040433 75j |

Sjabloon: Geen geselecteerd

Onderzoeken: Van 28-09-2010 t/m 24-11-2010

Bepaling	09246 28-09-2010 13:10 P.A.M. de Vri	09567 28-09-2010 14:34 P.A.M. de Vri	10225 28-09-2010 18:05 P.A.M. de Vri	10451 28-09-2010 20:50 P.A.M. de Vri	10732 29-09-2010 06:42 P.A.M. de Vri	09901 29-09-2010 08:00 P.A.M. de Vri	13764 29-09-2010 14:57 P.A.M. de Vri	14376 29-09-2010 21:22 P.A.M. de Vri	14444 29-09-2010 22:28 P.A.M. de Vri	14669 30-09-2010 06:57 P.A.M. de Vri	12667 30-09-2010 08:00 P.A.M. de Vri	16441 30-09-2010 11:11 P.A.M. de Vri	17372 30-09-2010 14:57 P.A.M. de Vri	18028 30-09-2010 21:21 P.A.M. de Vri	18063 30-09-2010 21:40 P.A.M. de V
== HEMATOLOGIE ==															
Hemoglobine	9.9	-	-	-	-	-	-	-	-	-	8.8	-	-	-	-
Ht	0.44	-	-	-	-	-	-	-	-	-	0.41	-	-	-	-
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MCV	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MCH	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MCHC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
RDW	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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Bezinking	**48**	-	-	-	-	**34**	-	-	-	-	-	-	-	-	-
C-Reactive Protein	**132**	-	-	-	-	**155**	-	-	-	-	**149**	-	-	-	-
Leucocyten	**11.4**	-	-	-	-	**11.7**	-	-	-	-	**13.1**	-	-	-	-
Dif Lymfocyt	-	-	-	-	-	-	-	-	-	-	**1.0**	-	-	-	-
Dif Monocyt	-	-	-	-	-	-	-	-	-	-	0.8	-	-	-	-
Dif Eosinofielen	-	-	-	-	-	-	-	-	-	-	0.1	-	-	-	-
Dif Baso	-	-	-	-	-	-	-	-	-	-	0.0	-	-	-	-
Dif Neutro	-	-	-	-	-	-	-	-	-	-	**11**	-	-	-	-
Trombocyten	**138**	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Protrombinetijd_INR	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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APTT Screening ZGT	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
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== CHEMIE ==															
Bilirubine totaal	15	-	-	-	-	14	-	-	-	-	**19**	-	-	-	-
Bilirubine direkt	-	-	-	-	-	-	-	-	-	-	**8**	-	-	-	-
Alkalische Fosfatase	**220**	-	-	-	-	**237**	-	-	-	-	**370**	-	-	-	-
Gamma GT	**670**	-	-	-	-	**707**	-	-	-	-	**558**	-	-	-	-
ASAT	**53**	-	-	-	-	38	-	-	-	-	32	-	-	-	-
ALAT	33	-	-	-	-	32	-	-	-	-	23	-	-	-	-
LD	**341**	-	-	-	-	**278**	-	-	-	-	**306**	-	-	-	-
Troponine T	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CK	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ureum	5.1	-	-	-	-	4.8	-	-	-	-	3.6	-	-	-	-
Kreatinine	59	-	-	-	-	50	-	-	-	-	56	-	-	-	-
Geschatte GFR (per 1,73m²)	86	-	-	-	-	104	-	-	-	-	91	-	-	-	-
Osmolaliteit	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Natrium	**130**	-	-	-	-	**134**	-	-	-	-	**131**	-	-	-	-
Kalium	3.5	-	-	-	-	**3.4**	-	-	-	-	**3.3**	-	-	-	-
Calcium	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fosfaat	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Magnesium	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
pH veneus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
pCO2 veneus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bicarbonaat veneus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Base Excess veneus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
pO2 veneus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
O2 sat. veneus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
pH arterieel	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
pCO2 arterieel	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bicarbonaat arterieel	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

A complete work-up

- ECG: Atrium flutter.
- bone marrow biopsy, was done to exclude malignancy. Her blood, stool, urine cultures and viral serology were all negative. a tuberculin test were negative.
- All serologic examination was negative. Chest radiogram showed cardiomegaly.
- An ultrasound scan of the abdomen showed no abnormalities.
- CT thorax: multiple pathologic mediastina lymphomas (see Picture 2)
- Pet scan: elevated uptake in multiple pathologic nodule high supraclavicular right and mediastina.
- Mediastinal lymph nodule biopsy: no malignant cells. non-specific reactive Para cortical hyperplasia

- Biopsy middle lung: no malignancy.
- Cytological punction thyroid gland nodule: normal
- Bronchoscopy: no tumor.

Serology

- anti-CMV IgG +, anti-CMV IgM -,
  anti-EBV-VCA IgM -, anti-EBV-VCA IgG +,anti-EBV-EBNA +
  anti-EBV-EA -
  anti-Legionella IgG -
  anti-Legionella IgM -
  anti-Coxiella burnetii -
  Borrelia –
  Ricketts: -
- ANA, ANCA negatief
  Mantoux test: negatief

Microbiologic tests

Feacal cultures: SSYC negative, triple feaces neg
Bloed, Urine cultures: negative

Legionella test: negative
Quantiferon TB gold test, Auramine color test : to sign of tbc

PCR M. tuberculosis complex: negative
PCR Non tuberculeous mycobacteries (NTM): negative

en voettekst"

X-Thorax: Cardiomegaly. Long vessels lighty increased in volume

Echo abdomen: slight steatosis.

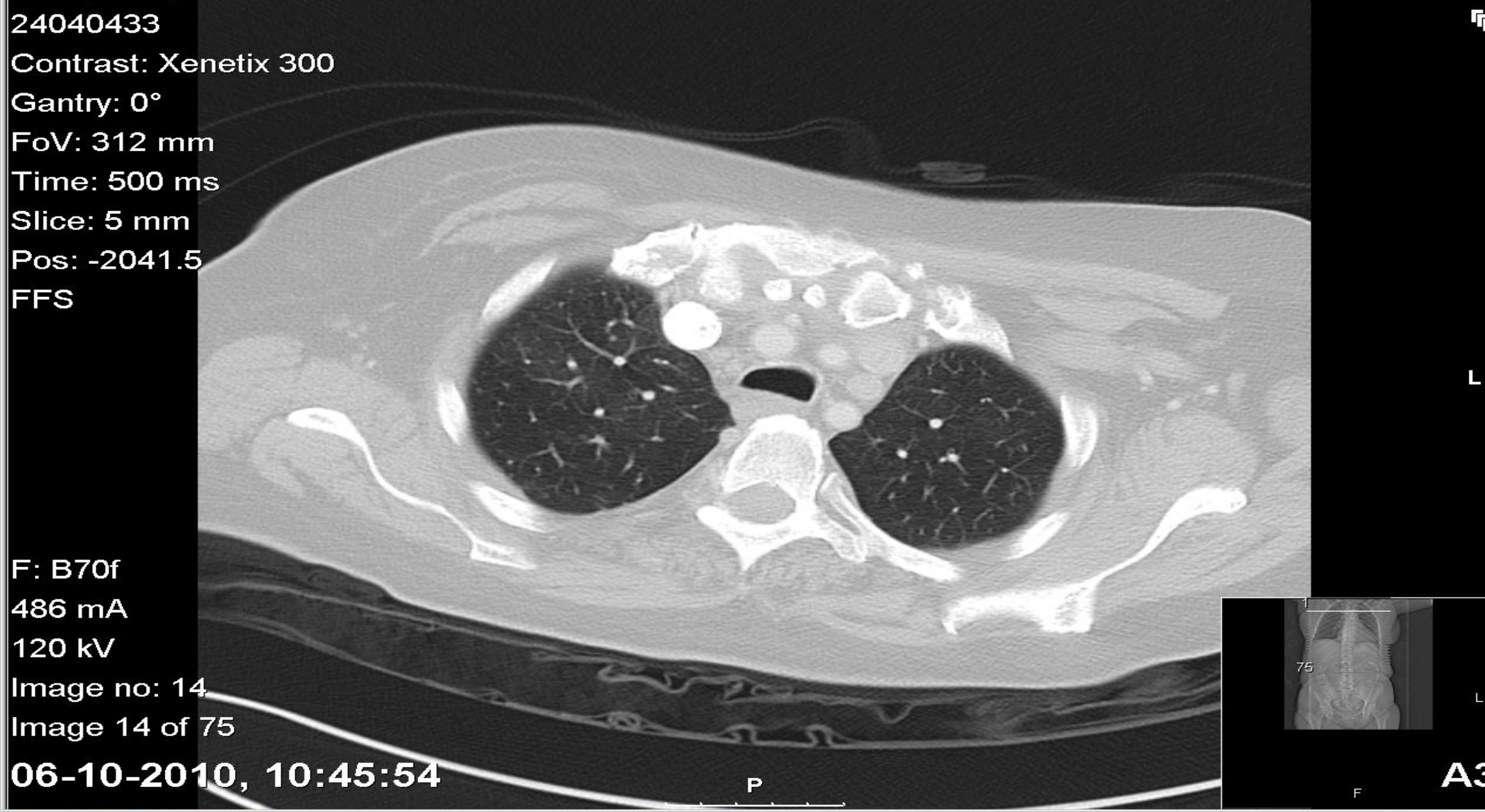
CT Thorax: Lymphoma in mediastinum with multiple lymph noduli in the lungs.

FDG-PET-SCAN WHOLE BODY

Multiple pathologic noduli neck left

supraclavicular right and mediastinal. Small uptake in the lung




24040433
Contrast: Xenetix 300
Gantry: 0°
FoV: 312 mm
Time: 500 ms
Slice: 5 mm
Pos: -2041.5
FFS
F: B70f
486 mA
120 kV
Image no: 14
Image 14 of 75
06-10-2010, 10:45:54
P
L
1
75
L
F
A3



Pathology

Punction supraclaviculair lymph noduli right:
no signs of malignancy or inflammation

Bronchoscopy: no tumor.

bioptsy middle long: no malignancy

Mediastinale klierbioptie: non specific reactive paracortical hyperplasy

- Antibioticum ceftriaxon, ciprofloxacin, doxycycline
- Pericarditis
- Recurrent fever attacks, not every day. At the begin of admission the heigth of fever heigher the at the end
- 2 times epiosodes of 4-5 dagen without fever

Hospital course

- She had daily fever attacks with hypotension during febrile episode. During admission of 7 weeks there were 2 periods of 4-5 days without fever. Most of the febrile attacks occurred at night or early in the morning. At the beginning of the hospital stay were the levels of fever higher than compared with the last weeks. She developed during 2nd week pericarditis. Except for the fever attacks she was hemodynamic stabile; only during a febrile attack she had hypotension and fatigue. She received Anakinra with clinical remission. There was an initial response without relapse.

Discussion

-*infection* all blood cultures, serologic tests are negative

-*paraneoplastic phenomenon*

elevetad BSE, suggestive for but not specificly for a malignancy. Lymph noduli in the longs, only one PET-positive

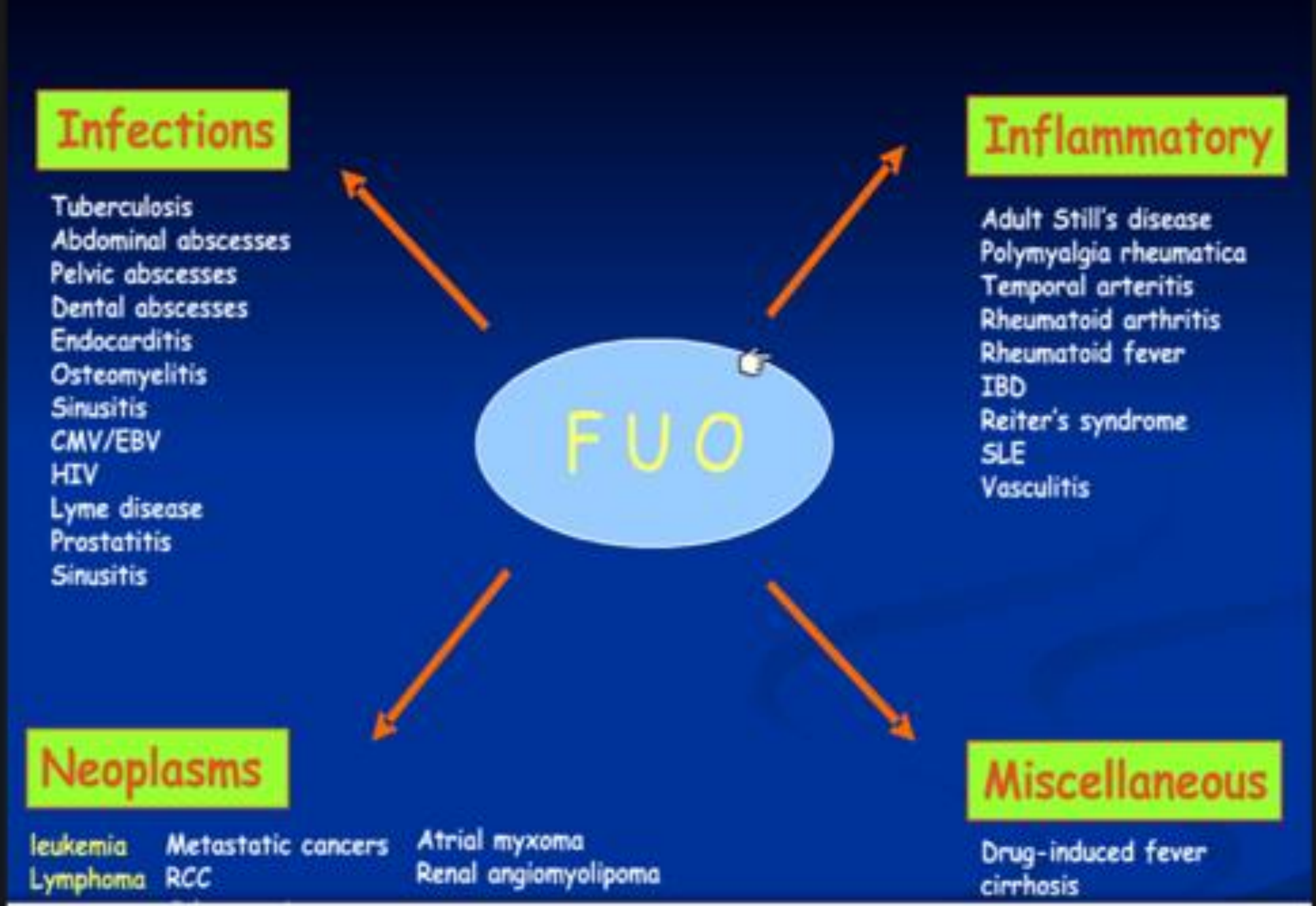
-*autoimmune*

ANA, ANCA negative, no rash, no artritis,

PET scan no signs of vasculitis

Conclusion

1 recurrent fever,
2 noduli longen, 1 PET positive.
Mediastinal lymph nodule bioptsy: no signs of malignancy
3nodus thyroid, cytologic punction: normal
4. pericarditis in history
5. atrium flutter wv Amiodarone 3 dd 200mg


Infections
Tuberculosis
Abdominal abscesses
Pelvic abscesses
Dental abscesses
Endocarditis
Osteomyelitis
Sinusitis
CMV/EBV
HIV
Lyme disease
Prostatitis
Sinusitis
Inflammatory
Adult Still's disease
Polymyalgia rheumatica
Temporal arteritis
Rheumatoid arthritis
Rheumatoid fever
IBD
Reiter's syndrome
SLE
Vasculitis
FUO
Neoplasms
leukemia
Lymphoma
Metastatic cancers
RCC
Atrial myxoma
Renal angiomyolipoma
Miscellaneous
Drug-induced fever
cirrhosis

DIFFERENTIAL DIAGNOSIS

When a patient has had recurrent fever episodes for more than 2 years, it is increasingly unlikely that these are caused by an infection or a malignant disorder. The differential diagnosis at th time may include numerous inflammatory disorders, such as juvenile rheumatoid arthritis, adult-onset Still's disease, inflammatory bowel disease, Schnitzler syndrome, and Behçet's disea in addition to the hereditary periodic fever syndromes (Table 113-2). Because the hereditary syndromes are rare (except for familial Mediterranean fever [FMF] in individuals with a distinct ethnic background), the more common diagnoses should be excluded first.

Table 113-2 — Differential Diagnosis of Periodic Fever

1. Hereditary (see Table 113-1)
2. Nonhereditary
    - **a.** Infectious
        - **i.** Hidden infectious focus (*e.g.*, aortoenteric fistula, Caroli's disease)
        - **ii.** Recurrent reinfection (*e.g.*, chronic meningococcemia, host defense defect)
        - **iii.** Specific infection (*e.g.*, Whipple's disease, malaria)
    - **b.** Noninfectious inflammatory disorder
        - **i.** Adult-onset Still's disease
        - **ii.** Juvenile chronic rheumatoid arthritis
        - **iii.** Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA)
        - **iv.** Schnitzler syndrome
        - **v.** Behcet's syndrome
        - **vi.** Crohn's disease
        - **vii.** Sarcoidosis
        - **viii.** Extrinsic alveolitis
        - **ix.** Humidifier lung, polymer fume fever
    - **c.** Neoplastic
        - **i.** Lymphoma (*e.g.*, Hodgkin's disease, angioimmunoblastic lymphoma)
        - **ii.** Solid tumor (*e.g.*, pheochromocytoma, myxoma, colon carcinoma)
    - **d.** Vascular
    - **i.** Recurrent pulmonary embolism
    - **e.** Hypothalamic
    - **f.** Psychogenic periodic fever
    - **g.** Factitious or fraudulent

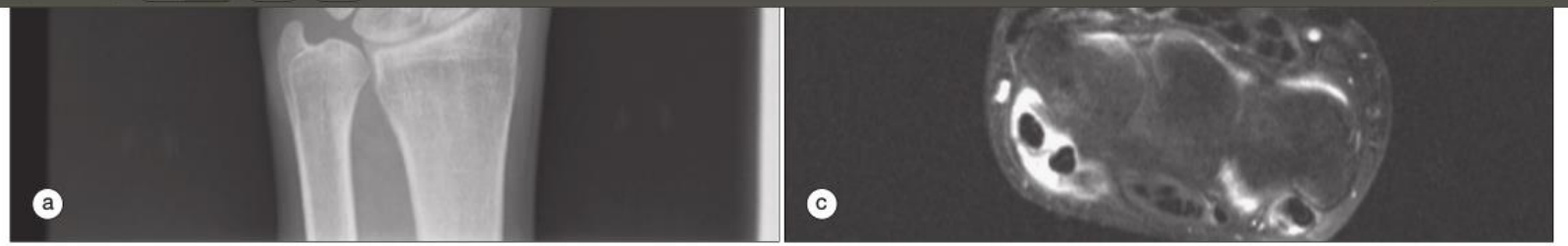


Fig. 84.2 Radiograph and MR image of wrist in patient with new-onset AOSD showing diffuse periarticular osteopenia (a) and carpal synovitis (b and c).



Fig. 84.3 Examples of maculopapular rash that worsened in the early evening hours: salmon pink lesions that (dis)appeared within hours of fever spikes (a) and more intense erythematous lesions that did not regress completely (b).

Rash

The classic skin manifestation is of a maculopapular rash consisting of flat salmon-pink skin areas that have small, confluent bumps. The rash is predominantly seen on the trunk and proximal extremities (Fig. 84.3) and often evanescent (i.e., pronounced during febrile periods and disappearing almost completely in between). Skin biopsies are not diagnostic and show dermal edema and perivascular infiltration by granulocytes and lymphocytes of the superficial dermis (Fig. 84.4) without deposition of immunoglobulins or complement factors.[35] Dermatographism (Koebner phenomena) is the occurrence of a linear erythematous skin reaction along a line of trauma and, although non-specific, is present in 30% to 60% of AOSD patients and more pronounced during the rash.[22,23] Other skin manifestations of AOSD are palpable purpura (with leukocytoclastic vasculitis on biopsy), folliculitis, erythema nodosum, and urticarial rash. Whether these truly represent disease activity or allergic (drug) reactions is unknown.

TABLE 87.1

Frequency (%) of clinical disease manifestations at initial evaluation in recent series of adult-onset Still disease

	Baxevanos[14]	Chen[15]	Laskari[16]	Riera[17]	Kong[18]	Franchini[19]	Zeng[20]	Lee[21]	Mitamura[22]	Cagatay[23]	Mehrpoor[24]	Singh[25]	Uppal[26]	Pay[27]	Evensen[6]	Appenzeller[28]	Crispin[29]
Country	Greece	China	Greece	Spain	China	Italy	China	Korea	Japan	Turkey	Iran	India	Kuwait	Turkey	Norway	Brazil	Mexico
Year	2012	2012	2011	2011	2010	2010	2009	2009	2009	2009	2008	2008	2007	2006	2006	2005	2005
No. in cohort	22	61	25	41	104	66	61	71	34	84	28	14	28	95	13	16	26
Age (yr)	32	30	32	38	33	37	38	40	41	33	25	30	28	27	34	31	29
Female (%)	32	52	48	61	66	58	74	88	65	70	75	36	79	53	20	46	42
Fever (>39°C)	100	100	96	100	100	95	100	100	94	95	100	100	100	99	100	100	100
Arthralgia	91	80	88	98	NA	100	NA	85	91	96	92	NA	100	100	NA	69	92
Arthritis	18	NA	60	88	90	79	82	NA	41	69	60	100	64	85	69	100	88
Rash	73	79	64	93	95	79	89	84	91	60	85	57	85	82	77	100	54
Lymphadenopathy	73	52	56	41	66	54	53	68	58	33	57	71	61	37	62	50	54
Hepatosplenomegaly	NA	NA	44	NA	44	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hepatomegaly	NA	21	NA	22	NA	41	13	30	27	38	NA	57	35	45	23	81	38
Splenomegaly	NA	64	NA	17	NA	38	38	37	64	29	32	57	57	42	23	31	46
Serositis	NA	NA	20	15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	23	NA	19
Pleuritis	NA	11	NA	15	NA	18	18	15	9	10	NA	7	17	22	NA	6	19
Pericarditis	NA	10	NA	12	NA	14	25	14	9	12	28	14	3	8	NA	13	19
Myalgia	NA	36	NA	NA	NA	70	28	70	50	13	NA	NA	NA	70	NA	50	61
Sore throat	73	84	56	90	78	58	72	57	85	65	93	36	57	66	62	56	65
Inclusion criteria	Yama	Yama	Yama	Yama	Yama	Yama	Yama	Yama	Yama	Cush	Yama	Yama	Yama	Yama	Yama	Cush	Expert

NA, not available; Yama, Yamaguchi.



Fig. 87.3 Example of the typical salmon-pink maculopapular rash affecting the extremities (a) and in more detail (b).

Pericarditis, pleural effusions, and transient pulmonary infiltrates have also been observed in patients with AOSD. Affected patients may complain of cough, pleuritic pain, or mild dyspnea. However, severe interstitial lung disease has been described, and some patients progress to acute respiratory distress syndrome.

Infrequent findings

Over the years, less common findings have been described: myocarditis and cardiac tamponade, aseptic meningitis and encephalitis, seizures, cranial neural palsies, uveitis, interstitial nephritis, collapsing glomerulopathy, renal amyloidosis, and macrophage activation syndrome.

Laboratory findings

The characteristic laboratory findings of AOSD are not pathognomonic, but its presence plus the clinical manifestations should help clinicians establish the diagnosis.

The laboratory profile of the disease is a reflection of the systemic inflammation and cytokine cascade present. The erythrocyte sedimentation rate and C-reactive protein are almost invariably elevated.[30] These are typically accompanied by leukocytosis (white blood cell count >10,000/mm^3) with a predominance of neutrophils (>80%), normocytic normochromic anemia (typically the anemia of chronic disease), and thrombocytosis (Table 87.3). These hematologic abnormalities may sometimes reach extreme levels and mimic primary hematologic disease. Bone marrow examination has been reported to show hyperplasia of granulocytic precursors in all patients and hypercellularity and hemophagocytosis in some.[16]

Abnormal liver enzymes (aspartate aminotransferase, alanine aminotransferase, and γ-glutamyltransferase) can be seen in up to 75% of patients,[16,37] are more frequent in patients with hepatomegaly, and may show a hepatocellular, cholestatic, or mixed pattern. Abnormal liver function is thought to be part of the inflammatory process of the disease itself and tends to normalize with remission of the disease, although concomitant use of potentially hepatotoxic treatments often complicates interpretation.[38]

Serum ferritin is markedly elevated in as many as 70% of patients.[37] The elevations correlate with disease activity and have been suggested to be a serologic marker for monitoring response to treatment.[39] Elevated serum ferritin levels, higher than five times the upper limits of normal (40 to 200 ng/mL), may suggest the presence of the disease with 80% sensitivity and 46% specificity; when combined with a decrease in the proportion of glycosylated ferritin (<20%), the specificity rises to 93%.[40]

Absence of antinuclear antibodies and rheumatoid factor is one of the minor Yamaguchi criteria for AOSD.[41] However, a low titer of either occurs in less than 10% of patients without clinical implications and may reflect their presence in the general population. Complement consumption is rare, with C3 levels in general being normal to slightly elevated in the acute phase. The presence of anti–citrullinated peptide antibodies has been reported in only 1 of 23 patients tested, but there are no data about their role in AOSD.[17]

CLASSIFICATION AND DIAGNOSIS

No specific test is available that can be used for the diagnosis of AOSD. Therefore, the diagnosis is based on recognition of the specific disease pattern and exclusion of other causes: infection, malignancy (lymphoma), necrotizing vasculitis, autoinflammatory syndromes, Schnitzler syndrome, and some drug hypersensitivity reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome.[42]

Several criteria sets have been proposed for accurate diagnosis of AOSD[41,42,43] (Table 87.4). The Japanese criteria (Yamaguchi criteria[41]) have the highest sensitivity in patients with a definite diagnosis of AOSD.[44] The Yamaguchi criteria are hampered by a long list of diseases that must be excluded. The Fautrel criteria, which are more specific, require the not readily available measurement of glycosylated ferritin.[43]

MANAGEMENT

First-line treatment: nonsteroidal antiinflammatory drugs and glucocorticoids

AOSD is not a common disease, and therefore no randomized controlled trials have been performed. Treatment is based on information from observational studies. Therapeutic decisions should be based on the extent and severity of organ involvement.

Nonsteroidal antiinflammatory drugs (NSAIDs) are considered the first-line agents for AOSD. Patients with mild disease may respond. Twenty percent to 25% of patients achieved control with this therapy. No randomized trials have compared different NSAIDs. Aspirin (3 to 4 g daily), ibuprofen (800 mg four times daily), and naproxen (500 mg/twice daily) are selections for initial therapy. Of the NSAIDs, indomethacin (100 to 150 mg/day) seems to be the most effective. It is advisable that liver enzymes be monitored at the onset of therapy. Severe hepatitis has been suggested to be related to treatment with NSAIDs.[38]

Glucocorticoids are usually required to induce remission of symptoms. Patients with severe symptoms should be treated with glucocorticoids from the outset of therapy. The usual prednisone dose is 0.5 to 1 mg/kg/day. Intravenous pulse methylprednisolone (1000 mg/day times three) is reserved for life-threatening disease such severe hepatic involvement, disseminated intravascular coagulation, cardiac tamponade, and macrophage activation syndrome. No consensus has been reached on a therapeutic tapering scheme

temporomandibular, and hip joints has been described as well (Table 87.2). Synovial fluid shows mild to moderate inflammation in most patients. The histopathology is nonspecific and includes chronic synovitis with slight cell proliferation in the synovial lining layers, variable degrees of vascular engorgement, and moderate infiltrates with mononuclear cells.[30,31]

Early radiographic findings are usually nonspecific and consist of periarticular osteopenia and slight joint space narrowing. Carpal involvement with selective carpometacarpal and intercarpal space narrowing and focal erosive alterations leading to bone ankylosis has been suggested to be a differential diagnostic characteristic between AOSD and rheumatoid arthritis (RA)[32] (Fig. 87-1). Severe involvement of the hip joint leading to bilateral hip destruction has also been reported (Fig. 87.2).

TABLE 87.2

Frequency (%) of joint involvement in series of adult-onset Still disease

	Chen[15] (N = 61)	Riera[17] (N = 1)	Franchini[19] (N = 66)	Cagatay[23] (N = 84)	Pay[27] (N = 95)
Knee	74	61	65	51	56
Wrist	31	63	56	43	67
Ankle	33	32	52	39	39
Shoulder	26	27	27	13	15
Elbow	47	22	19	19	28
PIP	20	20	37	21	18
MCP	18	27	29	21	22
MTP	16	5	12	11	6
Hip	15	20	12	4	2
DIP	7	2	19	1	1
TMJ	2	2	8	NA	3

DIP, distal interphalangeal; MCP, metacarpophalangeal; MTP, metatarsophalangeal; NA, not available; PIP, proximal interphalangeal; TMJ, temporomandibular joint.

Myalgia is generalized and more often appears with exacerbations of fever. Inflammatory myopathy is found rarely, although a number of case reports have described an increase in muscle enzymes, but electromyography and muscle biopsy have not generally been suggestive of myositis.

Rash

The typical rash is an evanescent, salmon-pink, macular or maculopapular eruption that tends to occur with the fever (Fig. 87-3). The rash involves predominantly the trunk and extremities, but the palms, soles, and occasionally the face can also be involved. The Koebner phenomenon may be present in 30% to 60% of patients.[28,33] Skin biopsy specimens are not diagnostic and show slight inflammatory infiltrates of polymorphonuclear and mononuclear cells in the upper dermis.[34] Even though the histopathology is nonspecific, skin biopsy can be important in differentiating this disorder from vasculitis, Sweet syndrome, and other conditions. Atypical skin lesions that have been associated with AOSD include urticaria and persistent pruritic papules and plaques, which show a distinctive distribution of dyskeratotic keratinocytes in the cornified layers, as well as in the epidermis.[34]

Other frequent findings

Sore throat is common at initial evaluation (55% to 90%) and frequently recurs during a disease flare.[35] Examination shows severe, nonsuppurative pharyngitis with negative bacterial cultures.

Lymphadenopathy is detected in 33% to 73% of patients, with the cervical chain being most commonly involved. Splenomegaly may also be present (17% to 64%). The precise relationship between lymphadenopathy and other reticuloendothelial system manifestations such as hepatomegaly or splenomegaly is unclear; its combined presence with constitutional symptoms could lead to diagnostic confusion with lymphoma and even lymph node biopsy. Histopathologic evaluation shows a benign reactive hyperplasia with plasma cells and polymorphonuclear cell infiltration.[30,31]

Liver abnormalities, predominantly hepatomegaly and abnormalities in liver biochemistry, are present in approximately 20% to 90% of patients. Fulminant hepatic failure requiring liver transplantation is extremely rare.



Fig. 87.1 (a and b) Radiographs of the wrists of a patient with adult-onset Still disease showing narrowing of the carpometacarpal and intercarpal spaces and focal erosive alterations that have led to bone ankylosis in the left wrist.

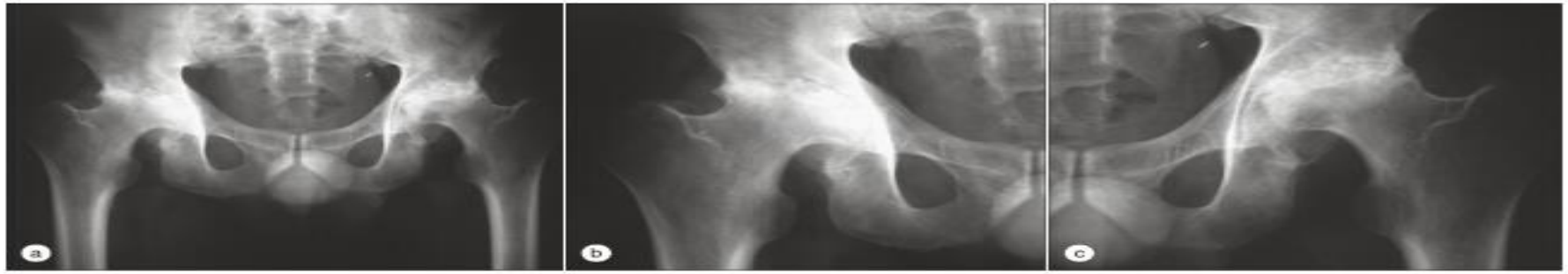


Fig. 87.2 (a to c) Radiographs of the pelvis showing the typical hip involvement leading to joint destruction.

	Cush et al (1987)[5]	Yamaguchi et al (1992)[6]	Fautrel et al (2002)[7]
Design	Single center, retrospective	Multicenter, retrospective	Single center, retrospective
Data analysis	Descriptive	Discriminatory statistical analysis	Logistic regression analysis
Cohort size	21	90	72
Disease duration	11.8 years	3.8 years	2.9 years
Case definition	Fever ≥ 39°C and arthralgia/arthritis with any 2 of: leukocytosis, JRA, rash, serositis/RES involvement	Clinical diagnosis upheld after case review by expert committee	Patients undergoing ferritin measurement and clinical diagnosis upheld after prolonged observation and case review by one expert
Excluded from analysis	RF > 1:80 ANA > 1:100	Non-definite cases after review (n = 56)	Non-definite cases after review
Comparator group	None	267 definite non-AOSD cases	130 definite non-AOSD cases
Criteria set	Fever ≥ 39°C and arthralgia/arthritis with any 2 of: leukocytosis, JRA, rash, serositis/RES involvement	*Major:* Fever ≥ 39°C for > 1 week, arthralgia > 2 weeks, maculopapular non-pruritic salmon-pink rash, leukocytosis ≥ 10,000/mm^3 with ≥ 80% neutrophils *Minor:* Pharyngitis or sore throat, lymphadenopathy, and/or splenomegaly, abnormal aminotransferases, negative rheumatoid factor or ANA assay	*Major:* Spiking fever ≥ 39°C, arthralgia, transient erythema, pharyngitis, neutrophils > 80%, glycosylated ferritin fraction < 20% *Minor:* Typical rash, leukocytosis ≥ 10,000/mm^3
Required	As above	At least 5 criteria, including 2 major	Four major criteria or 3 major and 2 minor criteria
Exclusion needed	None	Infections, malignancies, vasculitides	None
Sensitivity for set	Not analyzed	96%	81%
Specificity for set	Not analyzed	92%	98%

JRA, juvenile rheumatoid arthritis; RES, reticuloendothelial system; RF, rheumatoid factor; ANA, antinuclear antibody.

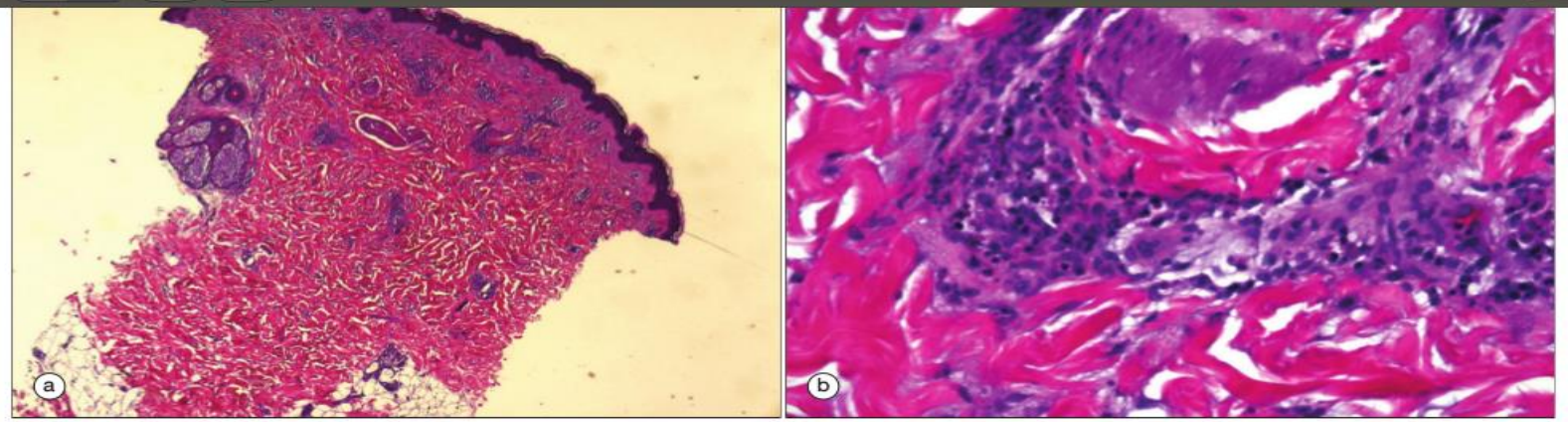


Fig. 84.4 Skin biopsy of maculopapular rash revealing normal appearance of the epidermis. The dermis shows full-thickness, perivascular infiltration of inflammatory cells, mostly lymphocytes and neutrophils. There is no evidence of vasculitis or extravasated red blood cells. Immunofluorescence showed no immunoglobulin deposits. (a, ×4; b, ×40.) *(Courtesy of Dr. Tormod Eggen, Department of Pathology, University Tromsø.)*

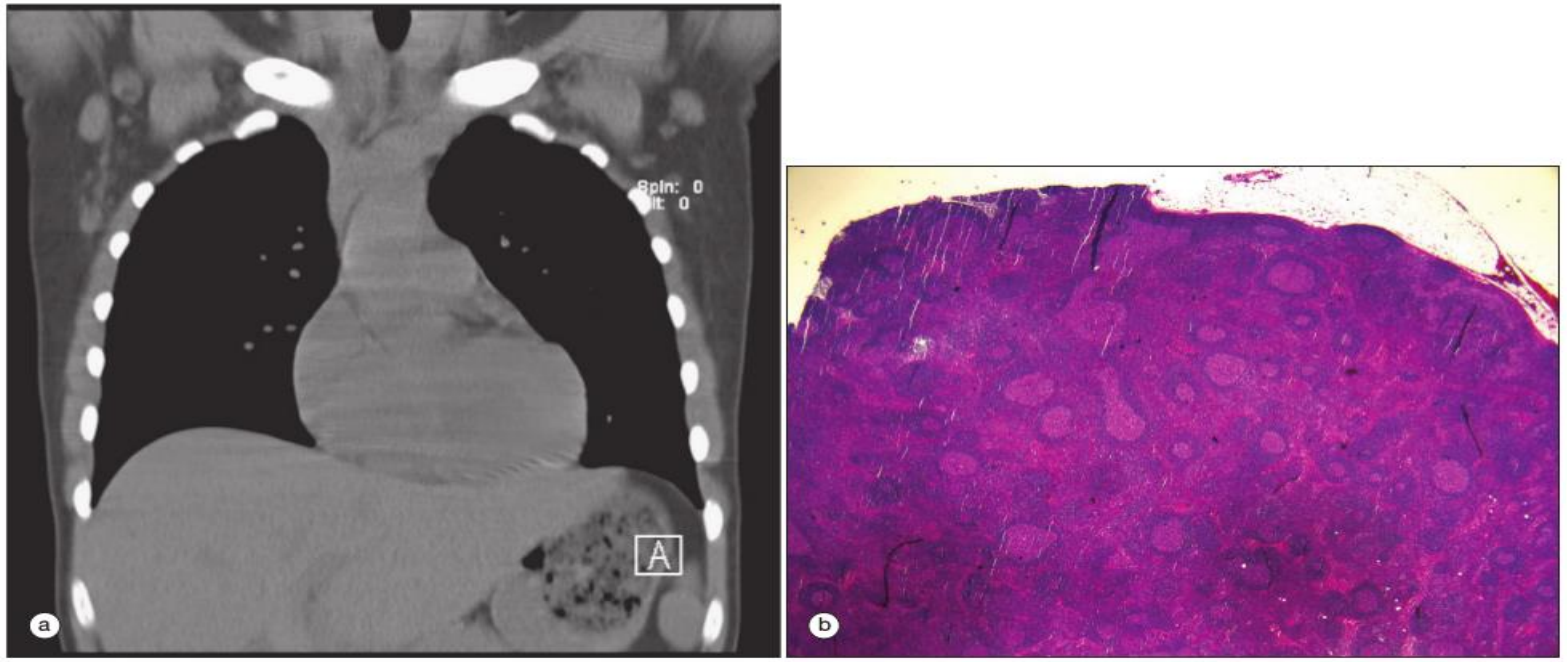


Fig. 84.5 (a) Bilateral axillary lymphadenopathy in AOSD as seen on CT. (b) Left axillary lymph node histology shows a regular node surface surrounded by perinodal fat. The subcapsular and medullary sinus show some histiocytosis. Throughout the lymph node the parenchyma is filled with follicles with well-demarcated germinal centers; no atypical cells are present. Immunohistochemistry revealed a normal distribution of CD3 (T cells) and CD20 (B cells) and negative findings for BCL2 (follicular lymphoma marker). *(Courtesy of Dr. Tormod Eggen, Department of Pathology, University Tromsø.)*

TABLE 87.3

Frequency (%) of laboratory findings at initial evaluation in recent series of adult-onset Still disease

	Baxevanos[14] (N = 22)	Chen[15] (N = 61)	Laskari[16] (N = 25)	Riera[17] (N = 41)	Kong[18] (N = 104)	Franchini[19] (N = 66)	Zeng[20] (N = 61)	Lee[21] (N = 71)	Mitamura[22] (N = 34)	Cagatay[23] (N = 84)	Mehrpoor[24] (N = 28)	Singh[25] (N = 14)	Uppal[26] (N = 28)	Pay[27] (N = 95)	Evensen[6] (N = 13)	Appenzeller[28] (N = 16)	Crispin[29] (N = 26)
Year of cohort	2012	2012	2011	2011	2010	2010	2009	2009	2009	2009	2008	2008	2007	2006	2006	2005	2005
Leukocytes >10^4	91	80	84	93	98	79	84	NA	74	84	92	NA	100	NA	91	100	85
Anemia	NA	18	64	24	69	38	15	NA	33	36	NA	50	54	75	36	62	NA
Thrombocytosis	NA	36	32	NA	77	20	NA	NA	NA	24	NA	71	82	48	46	NA	NA
Abnormal liver enzymes	86	70	60	51	62	79	23	NA	76	54	89	50	14	64	62	50	NA
Hypoalbuminemia	NA	72	NA	NA	NA	65	NA	NA	70	42	NA	NA	NA	42	37	NA	100
Elevated ESR	91	98	96	100	96	100	100	NA	89	94	NA	100	96	94	NA	NA	NA
Elevated CRP	91	100	100	100	92	NA	80	NA	NA	NA	NA	NA	NA	97	NA	NA	NA
Elevated ferritin	95	94	96	86	99	97	80	NA	100	95	71	87	89	89	62	56	NA
RF positive	5	7	4	0	5	0	11	NA	12	NA	4	10	0	NA	0	0	21
ANA positive	5	10	12	0	0	8	11	NA	23	NA	4	0	0	NA	0	0	13

ANA, antinuclear antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NA, not available; RF, rheumatoid factor.

TABLE 61.1
Interleukin-1 inhibitors in the treatment of rheumatic diseases

Disease	Biologic agent	Type of study	Primary outcome	Results
RA	Anakinra vs. placebo	RCT	ACR20 response criteria	Significant improvement[17]
RA	Anakinra vs. placebo	RCT	Genant and Larsen scores	Limits structural damage[18]
RA	Anakinra + MTX vs. MTX	RCT	ACR20 response criteria	Significant improvement[19]
RA	Anakinra + etanercept vs. etanercept	RCT	ACR50 response criteria	No difference, but increased frequency of SIE[20]
RA	Rilonacept + MTX vs. MTX	RCT	ACR20 response criteria	Nonsignificant effect*
RA	Canakinumab + MTX vs. MTX	RCT	ACR20 response criteria	Nonsignificant effect[25]
RA	AMG-108 + MTX vs. MTX	RCT	ACR20 response criteria	Nonsignificant effect[27]
RA	Pralnacasan + DMARDs vs. DMARDs	RCT	ACR20 response criteria	Nonsignificant effect[28]
AS	Anakinra	Case series	Multiple outcomes	Improvement[29]
AS	Anakinra	Case series	ASAS response criteria	ASAS20 in 5/20 patients[30]
PsA	Anakinra	Case series	Multiple outcomes	Improvement of arthritis but no effect on skin psoriasis[31]
SLE	Anakinra	Case series	Multiple outcomes	Improvement in ⅗ of patients[32]
Knee OA	Anakinra vs. placebo	RCT	WOMAC questionnaire	Nonsignificant effect[33]
Knee OA	AMG-108 vs. placebo	RCT	WOMAC questionnaire	Nonsignificant effect[35]
Gout	Canakinumab vs. triamcinolone acetonide	RCT	Pain on visual analog score	Significant improvement[39]
Gout	Canakinumab vs. triamcinolone acetonide	2 RCTs	Pain on visual analog score + time to new flare	Significant improvement and reduction of new flares[40]
Gout	Canakinumab vs. colchicine	RCT	Prophylaxis for flare	Significant reduction of new flares after initiation of allopurinol[41]
Gout	Rilonacept	Placebo controlled†	Pain on visual analog score	Improvement[42]
Gout	rilonacept vs. placebo	2 RCTs	Prophylaxis for new flares	Significant reduction of new flares[43,44]
Pseudogout	Anakinra	Case reports and patient series	Multiple outcomes	Improvement and prevention[45,46]
SOJIA	Anakinra	Case series	Multiple outcomes	Improvement[47,48]
AOSD	Anakinra	Case series	Multiple outcomes	Improvement[49]
FCAS, MWS	Anakinra	Case series	Multiple outcomes	Improvement[50]
FCAS	Rilonacept	Case series	Multiple outcomes	Improvement[51]
FCAS, MWS	Rilonacept	2 RCTs	Composite validated score	Significant improvement[52]
CAPS	Canakinumab	Open label	Multiple outcomes	Improvement[53]
CAPS	Canakinumab	Phase 3, open label	Multiple outcomes	Improvement[54]
Behçet uveitis	Gevokizumab	Case series	Ophthalmologic evaluation	Improvement[55]

*Unpublished study.
†Nonrandomized, single-blind study.
ACR, American College of Rheumatology; AOSD, adult-onset Still disease; AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis international Society; CAPS, cryopyrin-associated periodic syndromes; FCAS, familial cold autoinflammatory syndrome; HAQ-DI, health assessment quality-disability index ; MWS, Muckle-Wells syndrome; OA, osteoarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomized placebo-controlled clinical trial; SOJIA, systemic-onset juvenile idiopathic arthritis; WOMAC, Western Ontario–McMaster Universities Osteoarthritis Index.

Systemic-onset juvenile idiopathic arthritis and adult Still disease

Treatment with anakinra was reported to be dramatically successful in nine patients with refractory systemic-onset juvenile idiopathic arthritis (SOJIA).[47] A recent observational study indicated that only 40% of patients with SOJIA had a marked and persistent response to anakinra that led to a reduction or discontinuation of co-medications, including corticosteroids. A higher neutrophil count and lower number of active joints were associated with a good response to anakinra.[48] Anakinra has been reported to be effective for adult Still disease, with responses that could be even better than those for SOJIA.[49] Currently in phase 3 clinical development, canakinumab was recently granted E.U. and U.S. orphan drug status for this condition, as well as for cryopyrin-associated periodic syndromes (see the next section). Early clinical trials have shown that administration of canakinumab every 2 weeks is safe and effective and thus offers a considerable advantage over anakinra.

Interleukin-1 inhibition for periodic fever syndromes

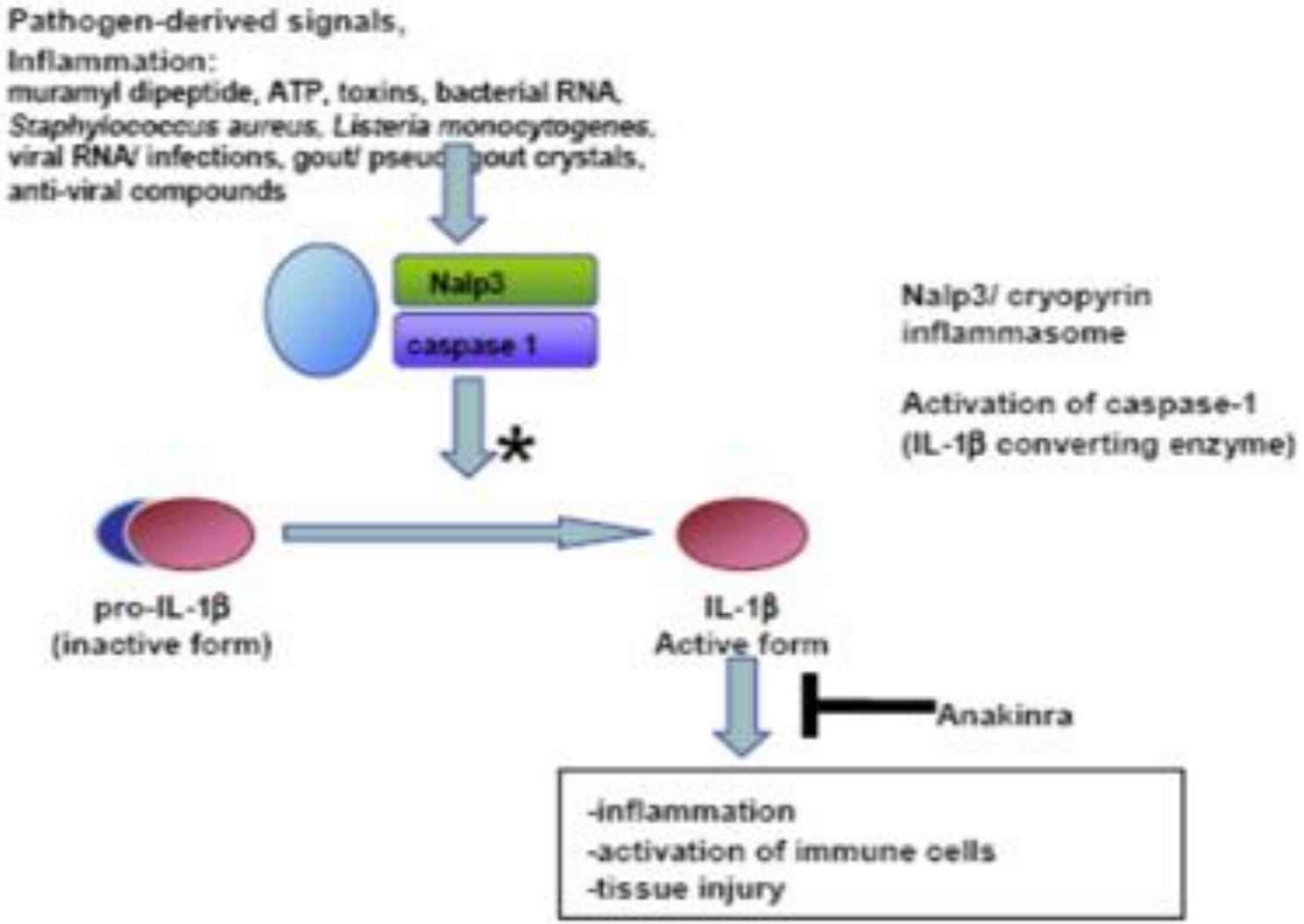
The term "cryopyrinopathies" or "cryopyrin-associated periodic syndromes" (CAPSs) was coined for a group of inherited disorders that includes neonatal-onset multisystem inflammatory disease (NOMID; also known as chronic infantile neurologic, cutaneous, articular syndrome [CINCA]), Muckle-Wells syndrome (MWS), and familial cold autoinflammatory syndrome (FACS), a condition characterized by recurrent episodes of fever and inflammatory responses in multiple organs. All these diseases have been associated with mutations in the *CIAS1* or *NLRP3* gene, which encodes for cryopyrin or NALP3. Administration of anakinra to patients with MWS and FACS resulted in the cessation of symptoms within hours of the first injection along with a concomitant decrease in serum amyloid A, an acute-phase protein; normal levels were reached after 3 days of treatment.[50] Significant improvement in NOMID/CINCA with anakinra has also been reported. Rilonacept has likewise been tested with success in patients with FACS.[51] These favorable results were confirmed by two consecutive randomized, placebo-controlled phase 3 clinical trials that included 47 adults with CAPS. The treatment was well tolerated except for injection site reactions and upper respiratory tract infections.[52] These results led to the approval of rilonacept by the Food and Drug Administration for the treatment of FACS and MWS in adults or children 12 years or older. Canakinumab was administered in an open-label clinical trial as a single subcutaneous injection, with redosing on relapse in seven patients with CAPS. All patients achieved a complete response within 24 hours following canakinumab administration according to physician assessments. The response was sustained for a median time of 49 days.[53] The 2-year results of a multicenter, open-label

Treatment
start with Anakinra (Recombinant Human Interleukin-1 Receptor Antagonist)



Figure 2 Therapeutic algorithm for AOSD.

Activation of the Nalp3 inflammasome results in activation of caspase 1 and subsequent conversion of IL-1β to its active form, resulting in immune activation, inflammation, and tissue injury.



Shinkai et al. Cryopyrin-associated periodic syndromes(CAPS) and autoinflammation CED-2006-00525

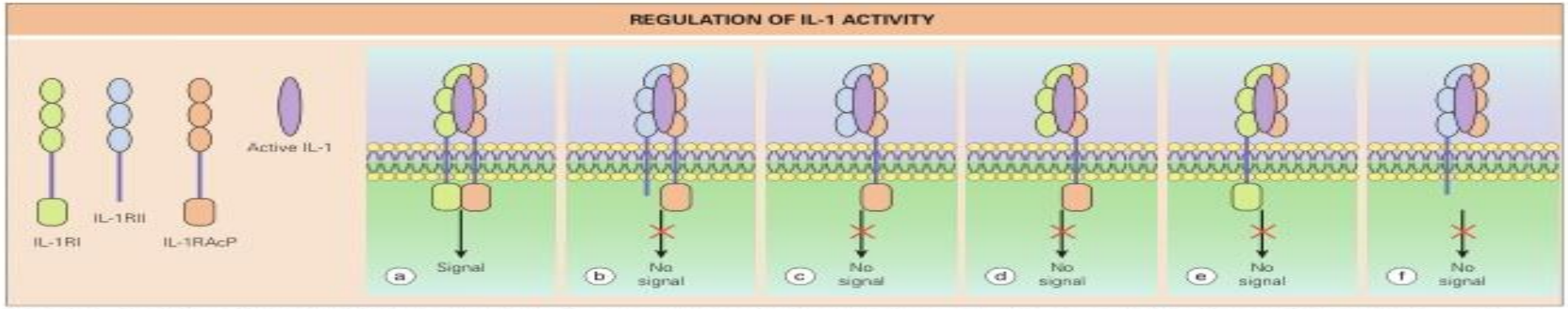


Fig. 61.1 Regulation of interleukin-1 (IL-1) activity by both membrane-bound and soluble forms of IL-1 receptors. (a) The biologic activities of IL-1, including membrane-bound pro-IL-1α, mIL-1α, and mIL-1β, are mediated by binding to the cell surface receptor IL-1RI. Binding of IL-1 induces a conformational change in the extracellular component of IL-1RI that enables its interaction with IL-1RAcP, which is required for intracellular signaling. IL-1RII might act only as a decoy receptor either (b) on the cell surface or (c) as sIL-1RII in the extracellular environment after enzymatic cleavage of its extracellular domain. sIL-1RII contributes to IL-1 antagonism. IL-1RI (d) and IL-1RAcP (e) also exist as soluble forms that are produced by cleavage of the extracellular domain and alternative splicing, respectively. To date, the physiologic role of sIL-1RI is unclear. sIL-1RAcP can form an inactive complex with cell surface IL-1RI bound to IL-1 and (f) also increases the potency of sIL-1RII as an inhibitor of IL-1 action. IL-1RAcP, IL-1 receptor accessory protein; IL-1RI/II, IL-1 receptor type I/II; m, mature; s, soluble. *(From Gabay C, Lamacchia C, Palmer G. IL-1 pathways in inflammation and human diseases. Nat Rev Rheumatol 2010;6:232–41, copyright Nature Publishing group.)*

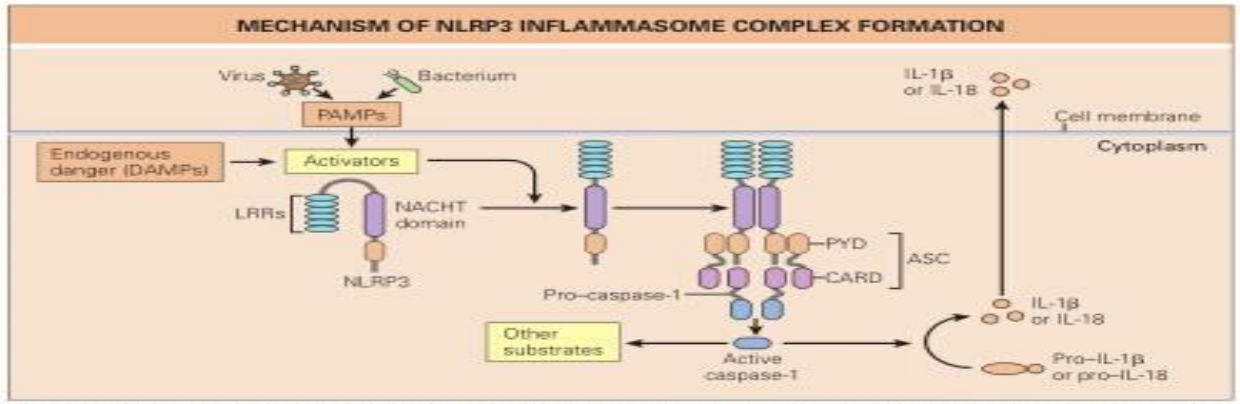


Fig. 61.2 Mechanism of NLR family, pyrin domain-containing 3 (NLRP3) inflammasome complex formation. Under healthy cellular conditions, NLRP3 is autorepressed because of an internal interaction between the NACHT domain and LRRs. This autorepression is removed in the presence of pathogen-associated molecular patterns (PAMPs) from microorganisms or damage-associated molecular patterns (DAMPs) from endogenous danger signals. This results in exposure of the NACHT domain. In turn, NLRP3 oligomerizes and recruits apoptosis-associated specklike protein containing a CARD (ASC; also known as PYCARD) and pro–caspase-1, which triggers the activation of caspase-1 and maturation and secretion of proinflammatory cytokines such as interleukin-1β (IL-1β) and IL-18. Other cytoplasmic proteins, such as enzymes of the glycolytic pathway, are also substrates of active caspase-1. CARD, caspase-recruitment domain; LRRs, leucine-rich repeats; NACHT, NAIP, CIITA, HET-E and TP1; PYD, pyrin domain. *(From Tschopp J, Schroder K. NLRP3 inflammasome activation: the convergence of multiple signalling pathways on ROS production? Nat Rev Immunol 2010;10:210–15, copyright Nature Publishing group.)*

American College of Rheumatology (ACR) response criteria[17] in preventing the progression of structural damage.[18] In patients with active RA despite methotrexate (MTX) therapy, the combination of anakinra and MTX resulted in better ACR responses than MTX alone did.[19] Safety data from a larger population indicate that anakinra in combination with different disease-modifying antirheumatic drugs (DMARDs) is safe, with a rate of serious infections slightly higher in the anakinra than in the placebo group (2.1% vs. 0.4%).[20] incidence of serious infections.[21] Use of anakinra in patients who had a previous incomplete response to tumor necrosis factor-α (TNF-α) inhibitors did not show any advantage either.[22]

Soluble interleukin-1 receptors

Administration of soluble IL-1RI (sIL-1RI) administered either by intraarticular or subcutaneous injection was devoid of significant effect in patients with RA.[23] Despite some interesting preclinical results, no data are avail-

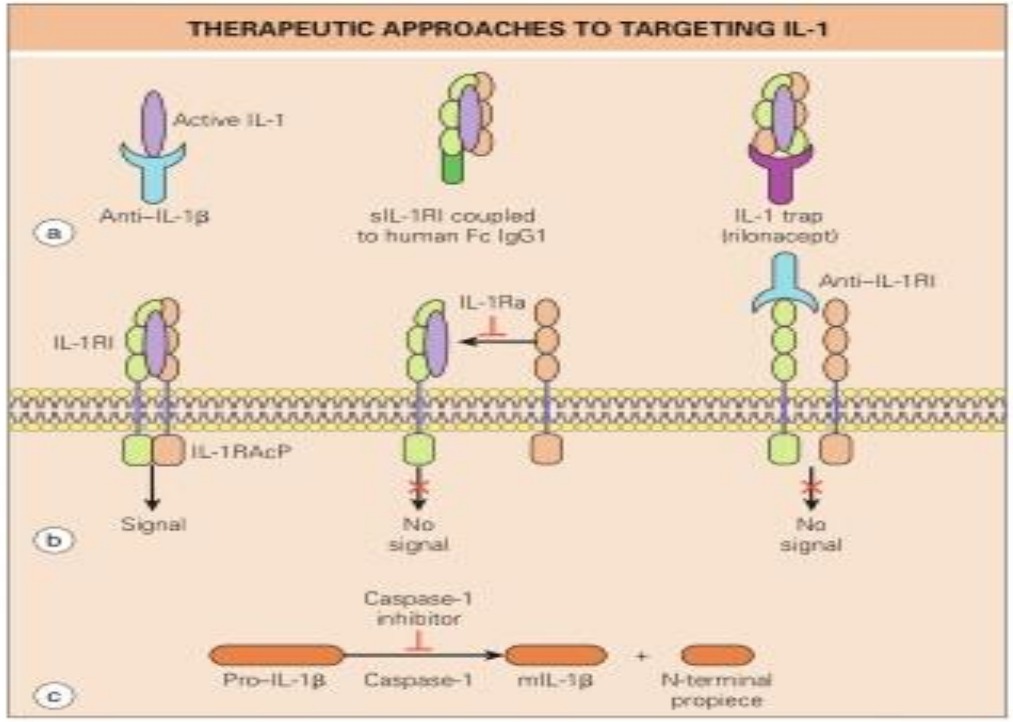


Fig. 61.3 (a) Anti-IL-1β, IL-1 trap (rilonacept), and sIL-1RI can block extracellular IL-1β. (b) Binding of active IL-1 to cell surface receptors can be inhibited by IL-1Ra and anti-IL-1RI antibodies. (c) Caspase-1 inhibitors can specifically inhibit the production of mature IL-1β. IL, interleukin; IL-1RAcP, IL-1 receptor accessory protein; IL-1RI, IL-1 receptor type I; m, mature; s, soluble. *(From Gabay C, Lamacchia C, Palmer G. IL-1 pathways in inflammation and human diseases. Nat Rev Rheumatol 2010;6:232–41, copyright Nature Publishing group.)*

IL-1 trap (rilonacept, Arcalyst) is a fusion protein containing some of the extracellular binding motifs of IL-1RI and IL-1RAcP coupled to the Fc fraction of human immunoglobulin IgG1. IL-1 trap has a prolonged circulating half-life ranging from 128 to 214 hours that permits once-weekly subcutaneous dosing. Administration of a murine form of IL-1 trap almost completely blocked the development of mouse collagen-induced arthritis.[24] Despite some encouraging results observed in a phase 1 trial,[23] a subsequent multicenter, randomized, double-blind, placebo-controlled phase 2 clinical trial failed to show a significant effect.

Monoclonal antibodies

The safety and efficacy of ACZ885 (canakinumab, Ilaris), an intravenously or subcutaneously infused, fully human monoclonal antibody that neutralizes the bioactivity of human IL-1β, were examined in a 6-week randomized, placebo-controlled, dose-escalating, clinical trial that included 32 patients

multicenter study in patients with RA receiving concurrent DMARDs. The ACR20 response rate was not significantly higher in patients treated with pralnacasan than in the placebo group.[28]

Despite positive results in animal models of arthritis, the results of clinical trials using anakinra and other IL-1 inhibitors have shown only modest therapeutic effects in patients with RA.

Ankylosing spondylitis

Anakinra treatment was moderately successful as assessed by clinical and magnetic resonance imaging (MRI) parameters in a 3-month open-label study that included nine patients with ankylosing spondylitis.[29] In another 24-week open-label clinical trial that included 20 patients with ankylosing spondylitis refractory to nonsteroidal antiinflammatory drugs, ASAS20, ASAS40, and ASAS70 responses were achieved by five, four, and two patients, respectively. No change was observed in the serum levels of C-reactive protein and MRI scores.[30]

Psoriatic arthritis

An open-label, proof-of-concept, single-center study of 12 patients with psoriatic arthritis demonstrated significant clinical benefits. After 12 weeks, 50% met the response criteria for psoriatic arthritis, but anakinra had no effect on the cutaneous manifestations of psoriasis.[31]

Systemic lupus erythematosus

Anakinra led to some positive results in a few patients with lupus arthritis.[32]

Osteoarthritis

The results of a randomized, double-blind, placebo-controlled study failed to show positive effects with a single intraarticular injection of anakinra for knee osteoarthritis (OA) at the 12-week evaluation.[33] This result is not unexpected in view of the short half-life of IL-1Ra. Of note, a positive trend ($P = .051$) on the Western Ontario–McMaster Universities Osteoarthritis Index (WOMAC) pain score was noted at day 4 in the 150-mg anakinra group versus placebo. In patients with an acute anterior cruciate ligament tear, administration of a single intraarticular injection of 150 mg anakinra led to a rapid and significant reduction in pain and improvement in function when compared with saline injection in a small 2-week randomized, double-blind clinical trial.[34] AMG-108, an antibody against IL-1R1, was administered subcutaneously or intravenously to patients with knee OA in a randomized double-blind placebo-controlled study. The AMG-108 group had statistically insignificant, but numerically greater improvement in pain than did the placebo group as shown by WOMAC pain scores (median change, −63.0 vs. −37.0, respectively).[35]

Further studies should investigate the rationale of IL-1 targeting for the signs and symptoms of OA and in the prevention of cartilage damage.

Crystal-induced arthritis

MSU and CPPD crystals are the agents responsible for gout and pseudogout, respectively. MSU and CPPD crystals can stimulate the NALP3 inflammasome and thus lead to pro-IL-1β processing and secretion of IL-1β.[36] More recently, it has also been shown that MSU crystals induce the release of IL-1α.[37] The basic calcium crystals that are associated

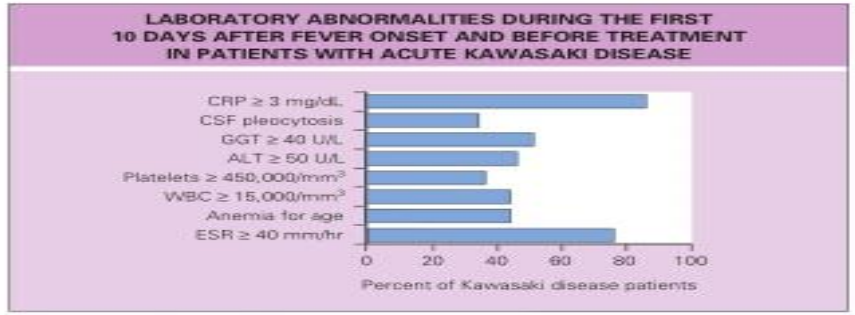


Fig. 160.5 Abnormal laboratory results seen in patients with acute Kawasaki disease. ALT, alanine aminotransferase; CRP, C-reactive protein; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate. GGT, γ-glutamyltranspeptidase; WBC, white blood cells.

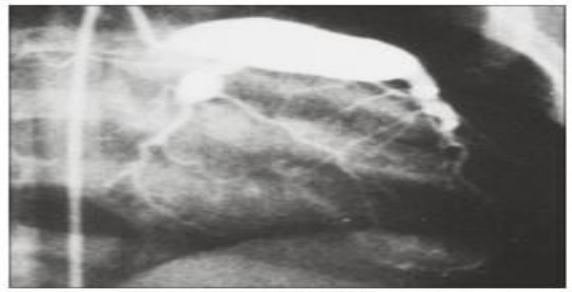


Fig. 160.6 Selective coronary angiogram showing a giant aneurysm of the left coronary artery.

arteries.[43] Myofibroblast infiltration with secretion of proinflammatory cytokines, matrix metalloproteinases, and elastases destroys the structural integrity of the vessel wall and can result in aneurysm formation (Fig. 160.6).[46] Three linked vasculopathic processes characterize the acute and chronic pathologic changes in the vessel wall and include an acute, self-limited necrotizing arteritis, a subacute or chronic vasculitis, and luminal myofibroblastic proliferation.

The necrotizing arteritis, which occurs during the first 2 weeks after onset of fever, is characterized by infiltration with neutrophils from the lumen of the vessel. Myocarditis is universal at this stage and can progress to fibrosis and scarring in the later stages.[43]

During the subacute/chronic vasculitis, which may begin within the first 2 weeks after fever onset, there is an infiltration of small lymphocytes, plasma cells, and eosinophils from the adventitial vasa vasorum, which progresses toward the lumen. Aneurysms of the coronary arteries with or without thrombosis can occur. Immunohistochemical testing shows a predominance of CD8+ T cells and macrophages infiltrating the vessel wall with secretion of matrix metalloproteinases during this stage.[46,49] Infiltration of immunoglobulin A–secreting plasma cells is also noted.[50]

A different vasculopathic process involves a progressive, asynchronous intraluminal stenosis mediated by vascular smooth muscle cell–derived myofibroblasts. This process is associated with intimal thickening, remodeling of aneurysms, thrombotic occlusion, and stenosis in the medium-sized arteries.

ETIOLOGY AND PATHOGENESIS

Most investigators agree that a microbial agent triggers the immune response that characterizes acute KD. Many infectious agents have been proposed and discarded as candidates for the causative agent of KD.[51] Intracytoplasmic inclusions that stain with a synthetic antibody constructed from sequences derived from KD plasma cells have been proposed as evidence of a viral cause.[52] It is possible that multiple agents trigger the syndrome in genetically susceptible hosts.

An understanding of the complex genetics of KD has been pursued through candidate gene studies, family linkage studies, and genomewide association studies.[53-56] A functional polymorphism in the inositol-1,4,5-trisphosphate 3-kinase gene that affects interleukin-2 signaling through the NFAT/calcineurin pathway confers increased susceptibility and also increased risk of aneurysm formation.[57] Genetic variation in the transforming growth factor-β signaling pathway confers increased risk of aneurysm formation.[58] Further studies are necessary to capture the sum of the genetic diversity that influences KD susceptibility and outcome.

TREATMENT AND MANAGEMENT

Based on large-scale clinical trials in the 1980s, the current recommended treatment for KD patients is a single intravenously administered dose of immunoglobulin (IVIG, 2 g/kg) in conjunction with high-dose aspirin (80 to 100 mg/kg/day).[59] After cessation of fever, most centers reduce the aspirin dosage to a low antiplatelet dosage of 3 to 5 mg/kg/day. The aspirin is continued until the ESR and platelet count have returned to the normal range. This approach, if implemented within the first 10 days after fever onset, reduces the incidence of coronary artery aneurysms from 25% to 5%.

IVIG resistance, defined as persistent or recrudescent fever (temperature of 38.0° C or higher) at least 36 hours after the end of the initial IVIG infusion, can occur in patients at highest risk of coronary artery damage.[60] Originally described as affecting only 10% to 15% of KD patients, IVIG resistance has now increased to 20% to 30% of patients in some regions of the United States and Japan.[61,62] Strategies to treat IVIG resistance have included a second infusion of IVIG, a single infusion of infliximab, corticosteroids, cyclosporine, and plasmapheresis.[63-66] Prospective identification of patients at risk of IVIG resistance would allow intensification of initial treatment.[67] Risk scores have been devised in Japan, but their application to populations outside of Japan has not been successful, possibly due to the mixed ethnic composition of the population.[60,68] A large, prospective, randomized multicenter trial in the United States examined the addition of pulsed methylprednisolone to IVIG in the initial treatment of KD patients, but no benefit was demonstrated.[69] In contrast, a prospective, randomized, open-label study of the addition of a 15-day course of steroids to primary therapy with IVIG in Japan in risk score–selected KD patients demonstrated improved coronary artery outcomes.[64] The use of corticosteroids at any point during the treatment of acute KD remains controversial.[70] In a retrospective study, patients treated with infliximab for IVIG-resistant KD had faster resolution of fever and fewer days of hospitalization but no difference in coronary artery outcome compared with patients treated with a second dose of IVIG.[71] A randomized, double-blind, placebo-controlled trial of infliximab plus IVIG for initial treatment of KD patients has completed enrollment, and data are currently being analyzed.

Arthritis persisting after treatment with IVIG usually responds well to naproxen or a single dose of infliximab. It is rare for patients to require treatment for arthritis beyond the subacute phase.

Management of cardiovascular complications should be undertaken by pediatric and adult cardiologists familiar with evolving treatment guidelines. Studies using historical controls suggest a benefit of warfarin therapy (to an international normalized ratio of 2.0 to 2.5) for patients with giant aneurysms (8 mm or more in internal diameter).[72,73] Antiplatelet therapy with aspirin and/or clopidogrel is recommended for all patients with persistent dilatation or aneurysms, although prospective trials have not been performed.[20]

Some centers perform echocardiography at 5-year intervals in all children and young adults after KD owing to the emerging recognition of arrhythmia, sudden death, myocardial fibrosis, and congestive heart failure in individuals with no documented coronary artery lesions during the acute phase of the illness.[74] Because arterial calcification is a common feature of KD vascular lesions, obtaining a computed tomographic coronary artery calcium score several years after acute KD may help identify individuals with significant vasculopathy.[75] Evidence-based guidelines for the long-term care and management of KD patients into adulthood are evolving.

TABLE 87.4
Criteria sets proposed to identify patients with adult-onset Still disease

	Cush et al. (1987)[43]	Yamaguchi et al. (1992)[41]	Fautrel et al. (2008)[42]
Design	Single center, retrospective	Multicenter, retrospective	Single center, retrospective
Data analysis	Descriptive	Discriminatory statistical analysis	Logistic regression analysis
Cohort size	21	90	72
Disease duration	11.8 yr	3.8 yr	2.9 yr
Case definition	Fever ≥39°C and arthralgia/arthritis with any 2 of leukocytosis, JRA, rash, serositis/RES involvement	Clinical diagnosis upheld after case review by expert committee	Patients undergoing ferritin measurement and clinical diagnosis upheld after prolonged observation and case review by one expert
Exduded from analysis	RF >1:80 ANA >1:100	Nondefinite cases after review (n = 56)	Nondefinite cases after review
Comparator group	None	267 definite non-AOSD cases	130 definite non-AOSD cases
Criteria set	Fever ≥39°C and arthralgia/arthritis with any 2 of leukocytosis, JRA, rash, serositis/RES involvement	*Major*: Fever ≥39°C for >1 wk, arthralgia >2 wk, maculopapular nonpruritic salmon-pink rash, leukocytosis ≥10,000/mm³ with ≥80% neutrophils *Minor*: Pharyngitis or sore throat, lymphadenopathy and/or splenomegaly, abnormal aminotransferases, negative rheumatoid factor or ANA assay	*Major*: Spiking fever ≥39°C, arthralgia, transient erythema, pharyngitis, neutrophils >80%, glycosylated ferritin fraction <20% *Minor*: Typical rash, leukocytosis ≥10,000/mm³
Required	As above	At least 5 criteria, including 2 major	Four major criteria or 3 major and 2 minor criteria
Exclusion needed	None	Infections, malignancies, vasculitides	None
Sensitivity for set	Not analyzed	96%	81%
Specificity for set	Not analyzed	92%	98%

ANA, antinuclear antibody; AOSD, adult-onset Still disease; JRA, juvenile rheumatoid arthritis; RES, reticuloendothelial system; RF, rheumatoid factor.

Other biologic agents

Limited evidence suggests that rituximab and abatacept may be effective in treating AOSD refractory to other biological agents. Canakinumab, a fully human monoclonal antibody against IL-1β with a half-life of 26 days, is promising. It is used for the management of cryopyrin-associated autoinflammatory syndromes caused by mutations in the NALP3 inflammasome. It has been used successfully in two patients with AOSD resistant to anakinra. Interestingly enough, canakinumab has been shown to be very effective in children with systemic JIA. Rilonacept (IL-1 Trap molecule, a soluble dimeric fusion protein) is another long-acting inhibitor of IL-1. It has been used successfully in four patients with AOSD.[45,46]

Treatment strategy for adult-onset Still disease

It is essential to keep in mind that therapeutic decisions should be based on the extent and severity of organ system involvement. The main options are NSAIDs, glucocorticoids, MTX, and biologic agents.

NSAIDs should be the initial therapy in patients with mild disease. Most patients will require treatment with glucocorticoids, especially those with fever, joints symptoms, or internal organ involvement. If glucocorticoids are required, we suggest adding MTX because long-term corticosteroid treatment is the rule. Pulse corticosteroid therapy is reserved for patients with life-threatening disease such as pericardial tamponade, myocarditis, diffuse intravascular coagulation, and macrophage activation syndrome. In patients with refractory disease, biologic agents, especially anakinra and tocilizumab, are promising[45,46] (Fig. 87.4).

Special issues regarding treatment

Pregnancy

Patients with AOSD are at increased risk for adverse outcomes of pregnancy. An increased rate of preterm birth and intrauterine growth retardation and a possible influence of disease activity on pregnancy outcome have been reported. AOSD may occasionally appear during pregnancy. Treatment with glucocorticoids is mandatory. In a patient known to have AOSD, pregnancy should be planned and treatment with immunosuppressors (MTX) stopped. A combined regimen consisting of glucocorticoids and NSAIDs is advisable. In the case of biologic drugs, it is recommended that they be stopped. Successful pregnancy and breastfeeding have been reported in a pregnant patient treated with anakinra.[33]



Fig. 87.4 Principal treatment regimens for adult-onset Still disease include NSAIDs, glucocorticoids, MTX, and biologic agents. AOSD, adult-onset Still disease; IL-1, interleukin-1; NSAID, nonsteroidal antiinflammatory drug; TNF, tumor necrosis factor.

Hip involvement

Hip involvement in patients with AOSD is a dramatic issue. The clinician should dismiss the possibility of osteonecrosis, fracture, and actual hip involvement by arthritis. Rapid diagnosis is required. If confirmed, corticosteroid injections are advisable. If the patient is not taking biologic drugs, this is recommended.

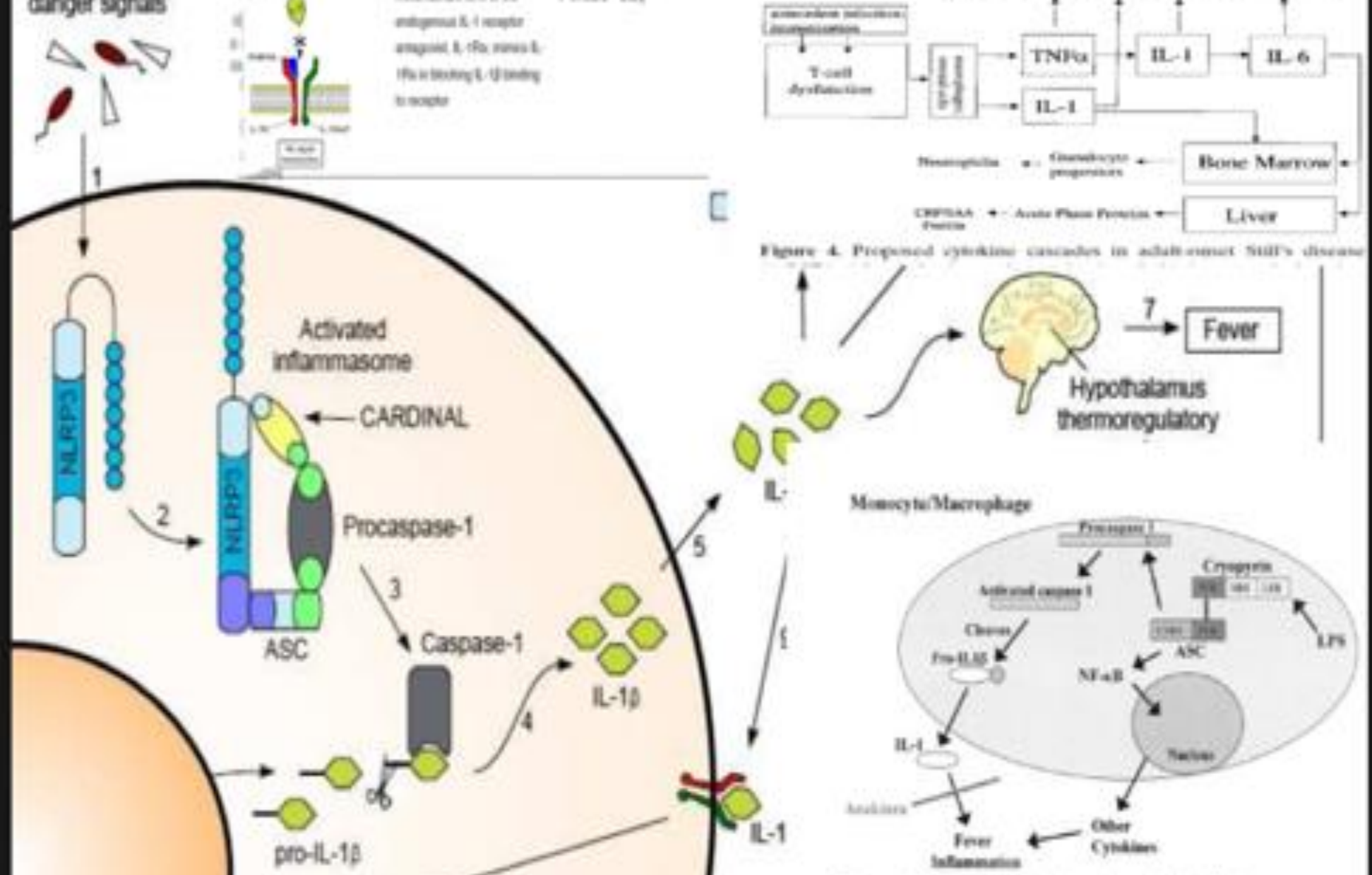


Figure 4. Proposed cytokine cascades in adult-onset Still's disease

Figure 5. Proposed mechanism of interleukin-1 (IL-1) receptor antagonist activity in cryopyrin (*NALP3*)-associated diseases. Cryopyrin binds to ASC, which activates caspase 1, resulting in IL-1 release. Anakinra competitively inhibits IL-1 binding to the IL-1 receptor. LPS = lipopolysaccharide.

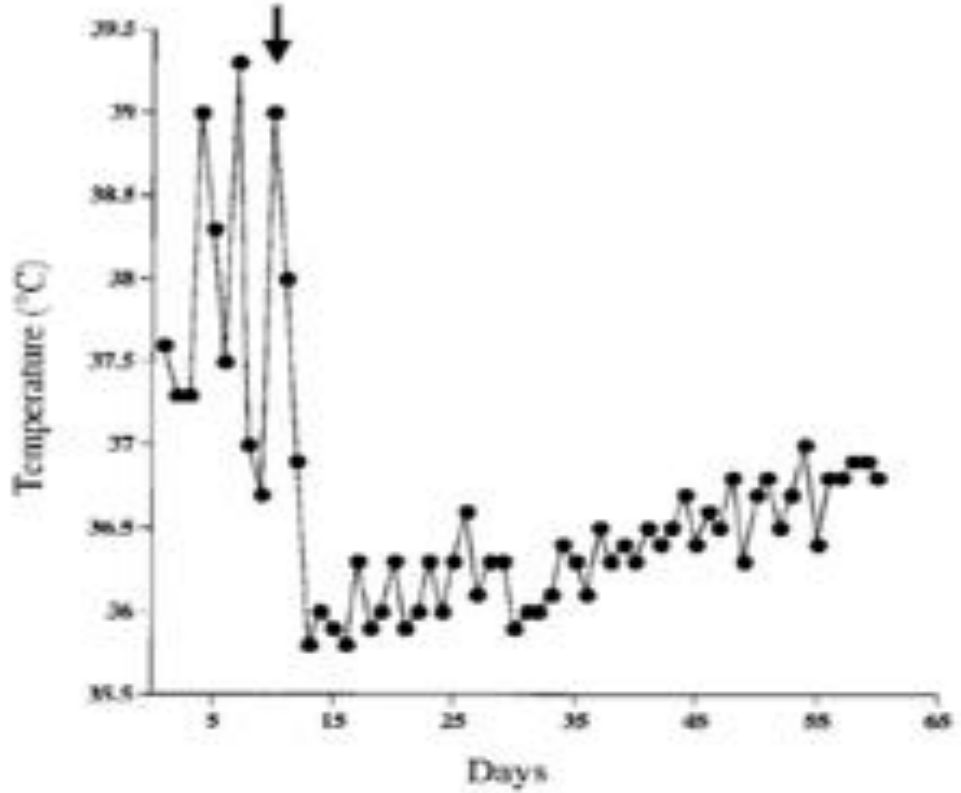
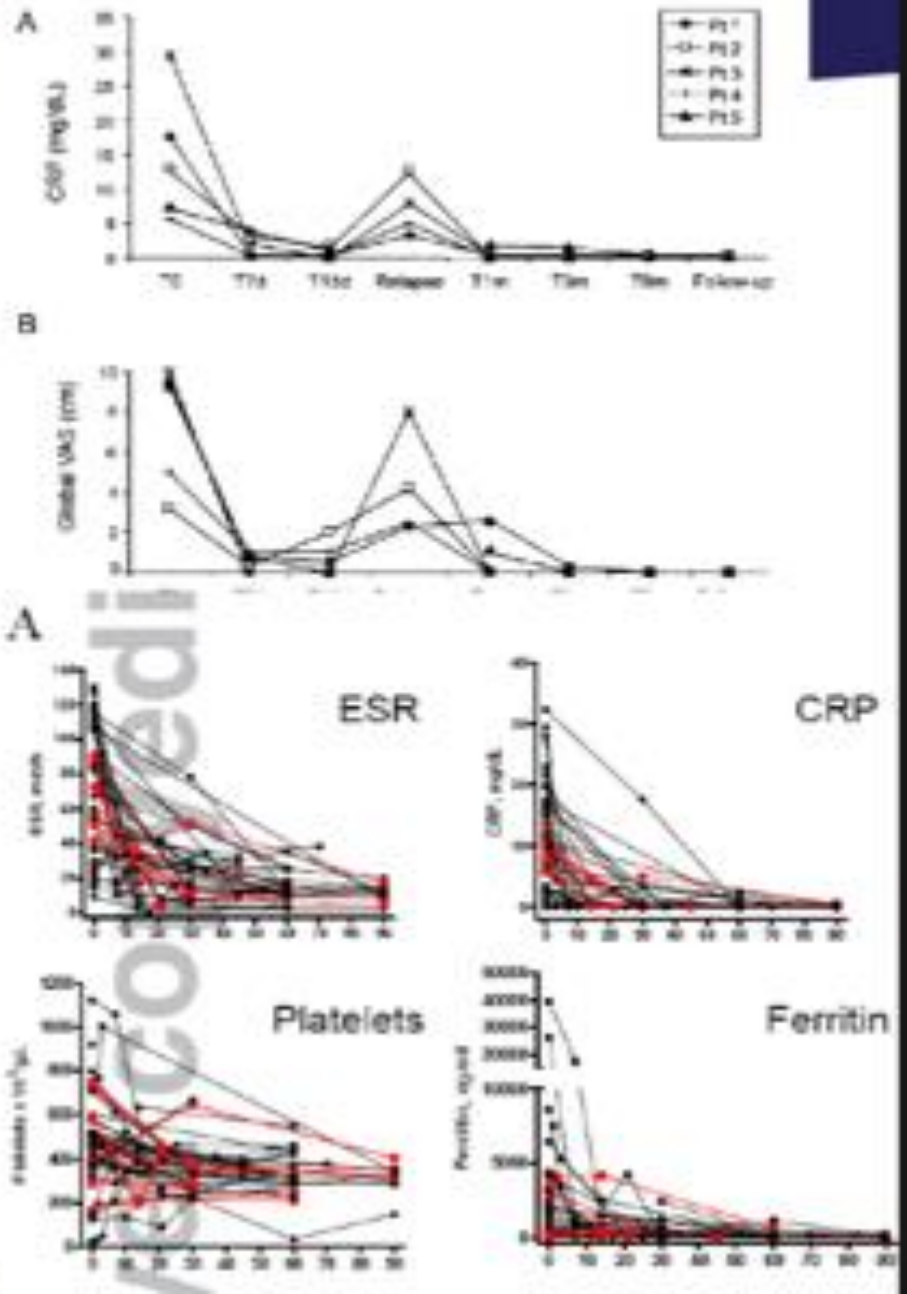


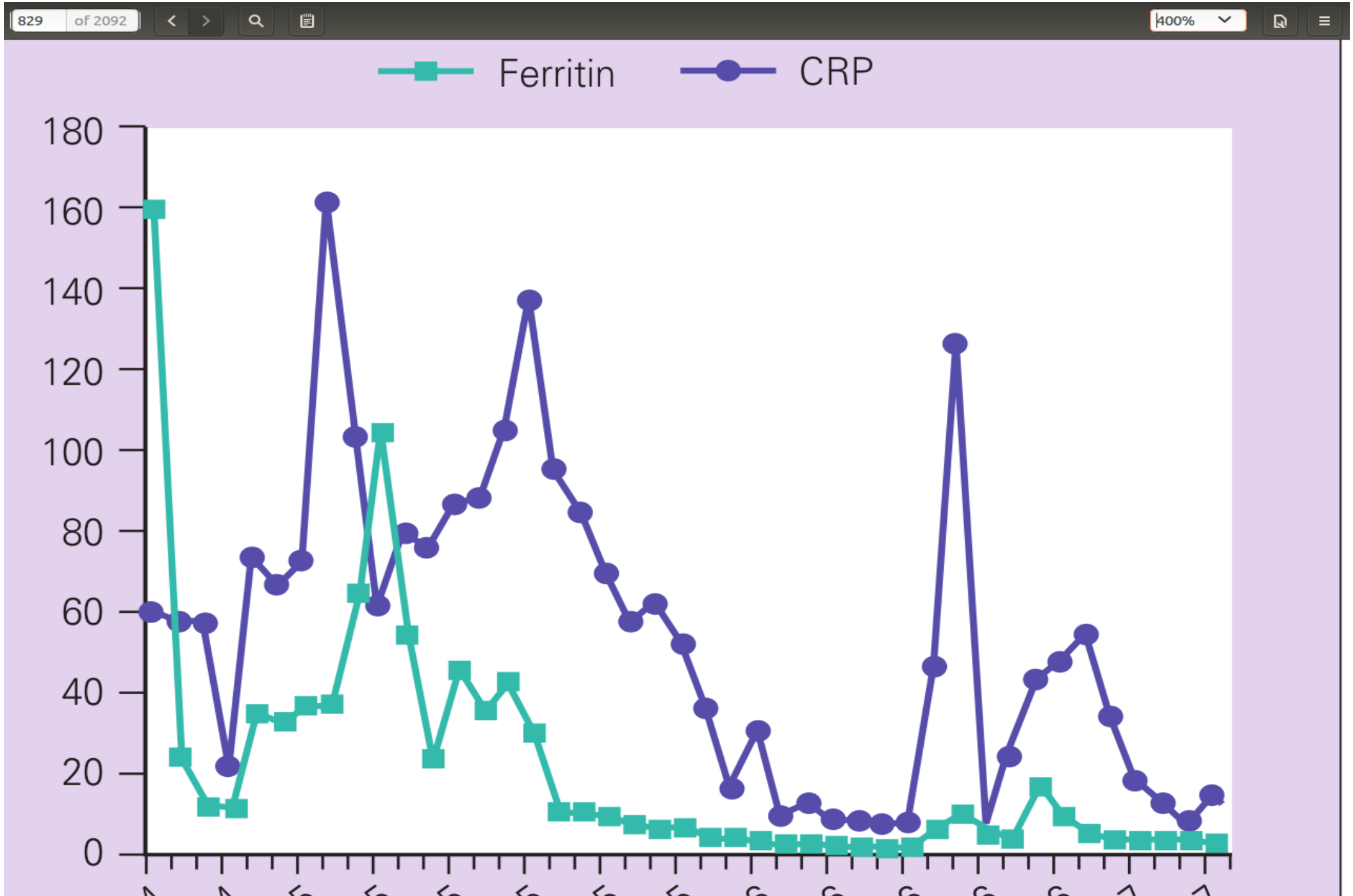
Figure 2. Temperature readings in the index patient. Recordings of oral temperature are shown for the specific day intervals shown. Arrow indicates the first injection of anakinra (100 mg).

Table 1 Evaluation of the mean number of fever attacks per month, days of fever per single attack, days of fever per month in the semester before anakinra and in the three semesters along with anakinra administration

	Before anakinra	During anakinra	Reduction (%)
Fever attacks per month	1.33 ± 0.82	0.77 ± 0.65	42.10
Days of fever per single attack	4.25 ± 1.98	3.50 ± 1.34	17.64
Days of fever per month	5.66 ± 3.88	2.72 ± 2.44	51.94

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Ferritin
CRP
180
160
140
120
100
80
60
40
20
0

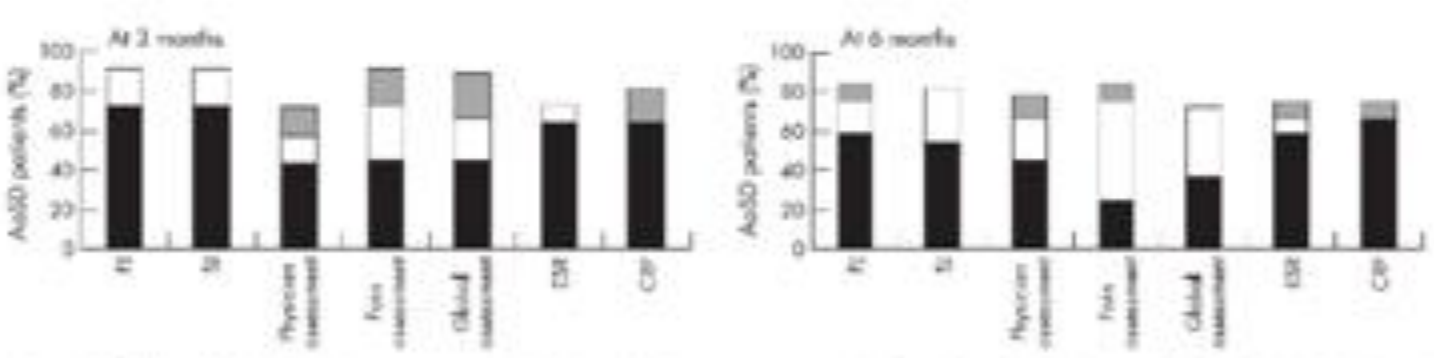


Figure 1 SoJIA and AoSD patients' response to analysis in an intention to treat analysis at 3 and 6 months. Percentage of SoJIA patients (top) and AoSD patients (bottom) who achieved a 20%, 50% and 70% improvement in the main disease activity variables at 3 and 6 months in an intention-to-treat analysis. AoSD, adult-onset Still disease; CHAQ, Childhood Health Assessment Questionnaire; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SJ, swollen joint count; SoJIA, systemic-onset juvenile idiopathic arthritis; TJ, tender joint count. Pain and disease activity levels for children were assessed by their parents.



Anakinra

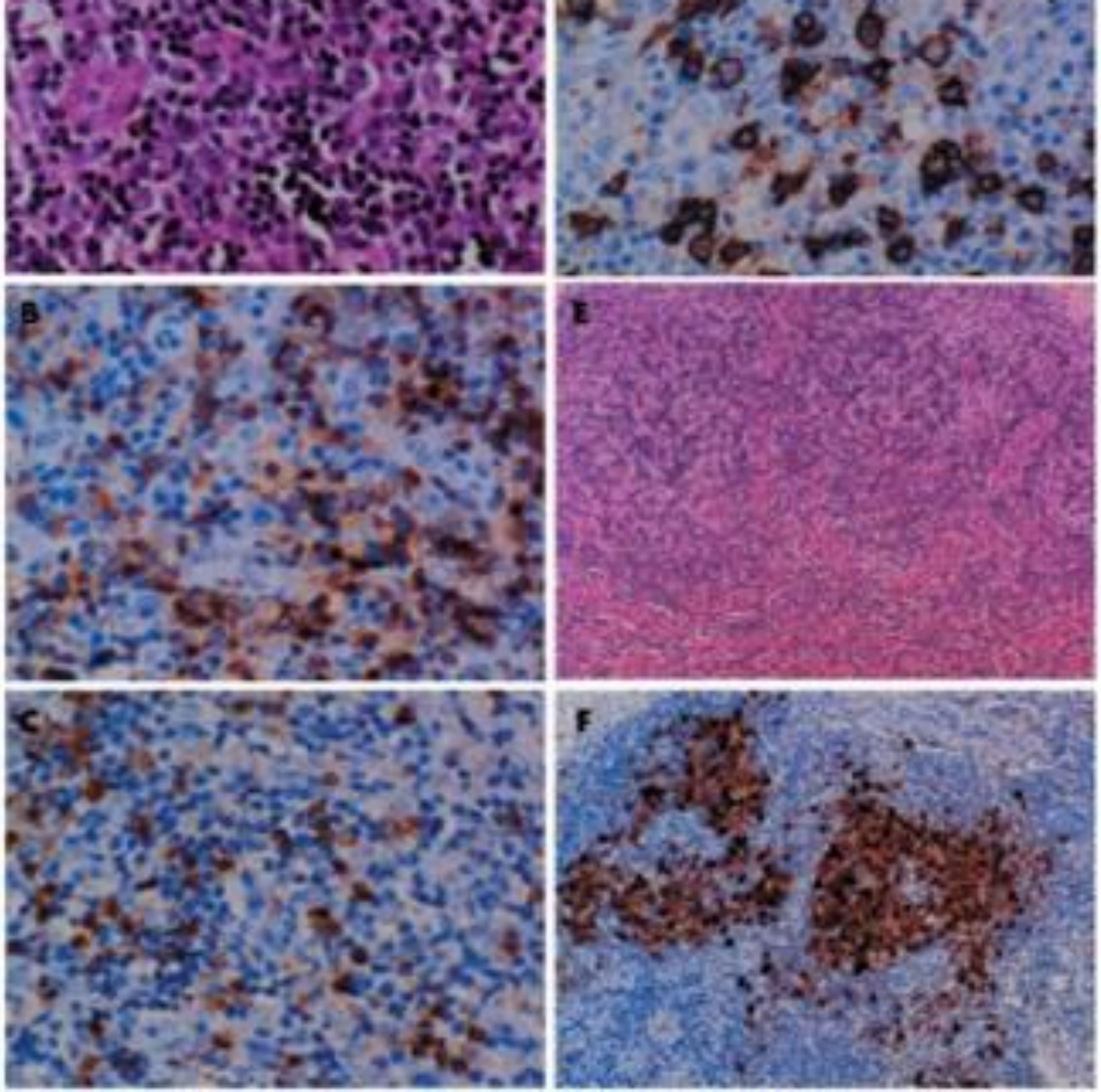
- Approved for moderate-to-severe RA
  - Patients who have failed on 1 or more DMARDs
  - Can be used in patients at risk for TB
  - Can be used alone or in combination with DMARDs but NOT TNF-blocking agents
- Binds to IL-1 receptor but has no biologic activity
- Daily SC injection
- Time to onset: 8-12 weeks
- Adverse events
  - Injection site reactions, infection, possible increased malignancy
- Monitoring
  - CBC monthly for 3 months, then every 3 months

Gartlehner G, et al. *J Rheumatol*. 2006;33:2398-2408; Leff L. *J Infus Nurs*. 2006;29:326-337; Kountz DB, Von Feldt JM. *J Fam Pract*. 2007;6:59e-73a.

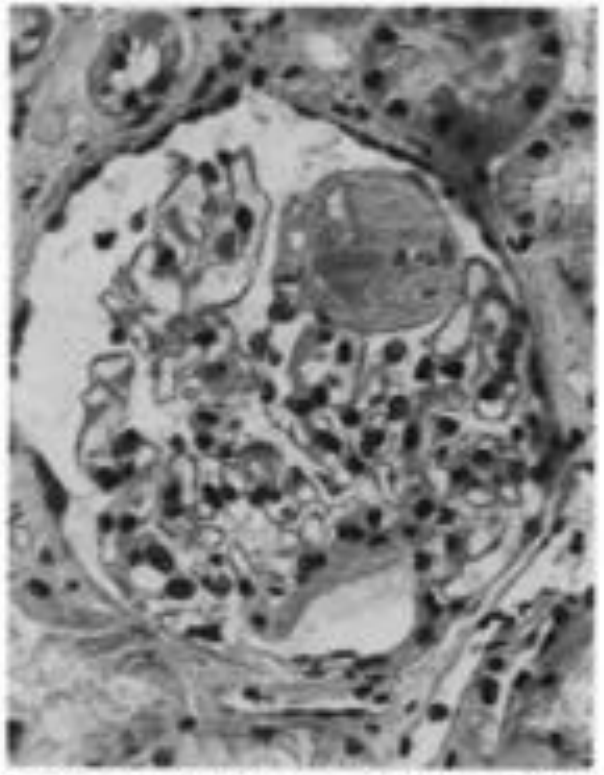
Prognosis

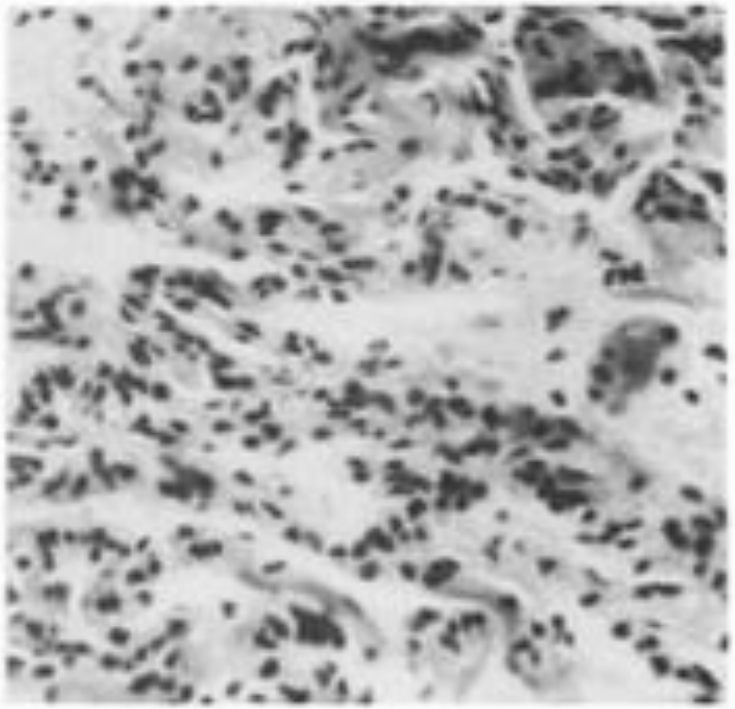
- Self limited
  - Most patients are in remission in one year
- Intermittent
  - Recurrent relapses
  - Relapses after years
  - Recurrent is milder than initial episode
- Chronic
  - Severe articular manifestations

  2/3 prosthesis



infiltrated by many small to medium sized lymphocytes, some large immunoblasts, plasma cells, and a few eosinophils. Haematoxylin and eosin (H&E) stain; original magnification, ×400. (B) CD4 expression in about three fifths of T cells. Immunoperoxidase stain; original magnification, ×400. (C) CD8 expression in about two fifths of T cells. Immunoperoxidase stain; original magnification, ×400. (D) CD20 expression in some of the large immunoblasts and a few small lymphocytes. Immunoperoxidase stain; original magnification, ×400. (E) Vascular transformation and sinus histiocytosis with mottled appearance. H&E stain; original magnification, ×100. (F) S-100 protein expression in the aggregated histiocytes. Immunoperoxidase stain; original magnification, ×200.

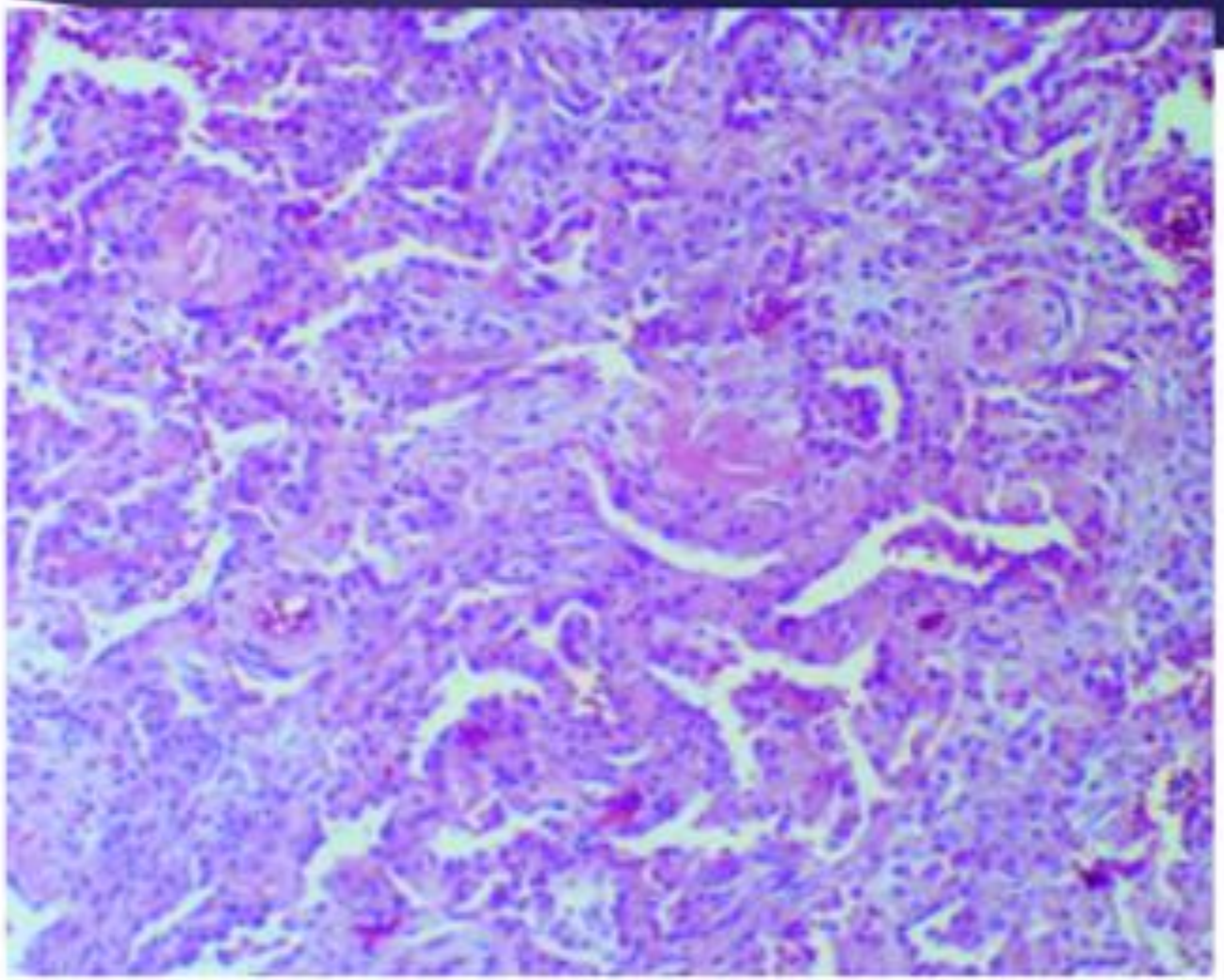




Kidney biopsy specimen showing amyloid deposition leading to complete destruction of some capillary hundles (haematoxylin-eosin).

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en voettekst

Wedge resection of left lower lobe (hematoxylin and eosin stain, original × 100).

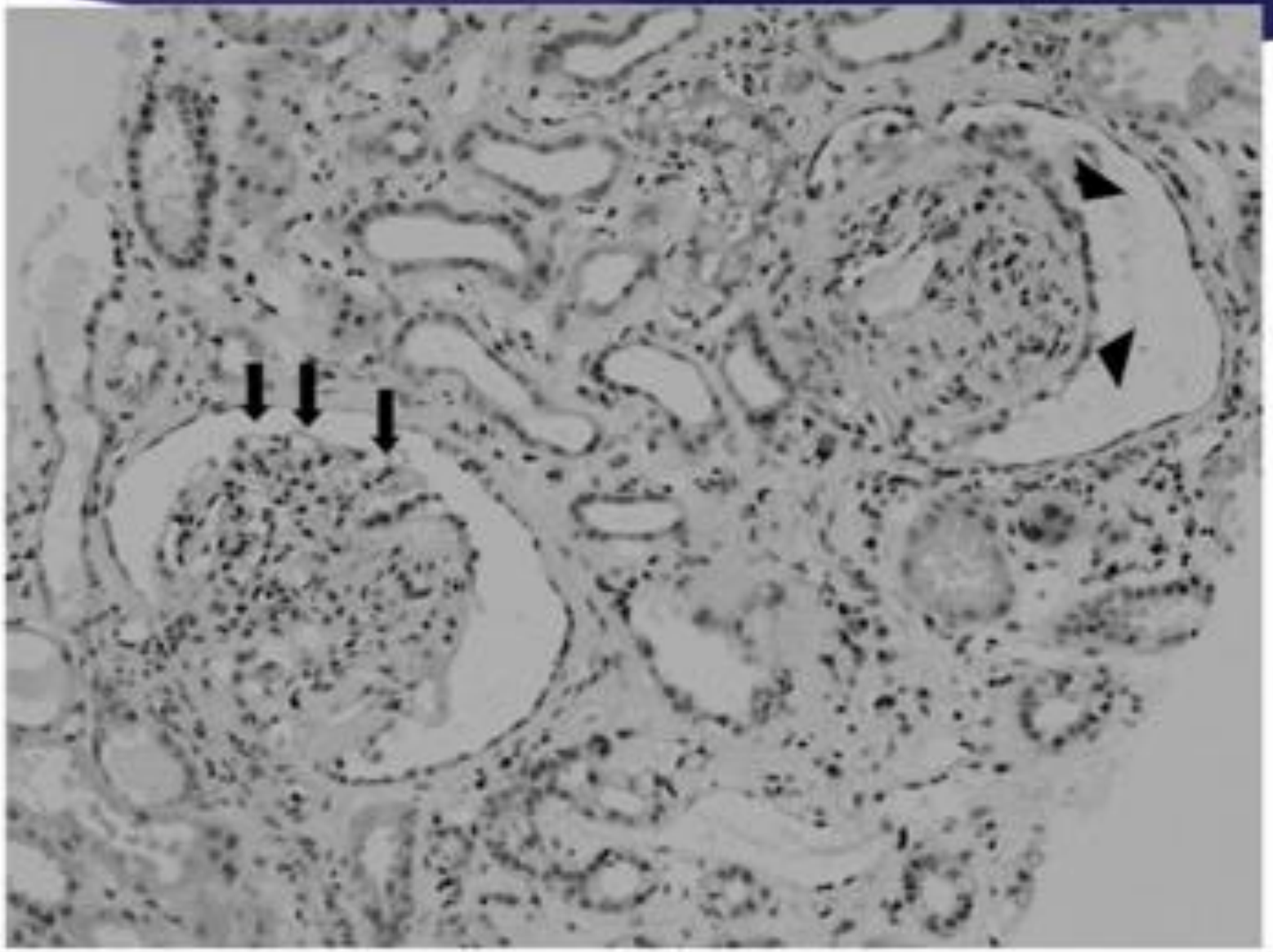


Stoica G S et al. Postgrad Med J 2002;78:97-98
diffuse interstitial fibrosis, hyperplasia of type II pneumocytes, fibroblast proliferation, and thickened alveolar

©2002 by The Fellowship of Postgraduate Medicine

en voettekst"

Renal biopsy: collapsing glomerulopathy.



Bennett A N et al. Rheumatology 2004;43:795-799

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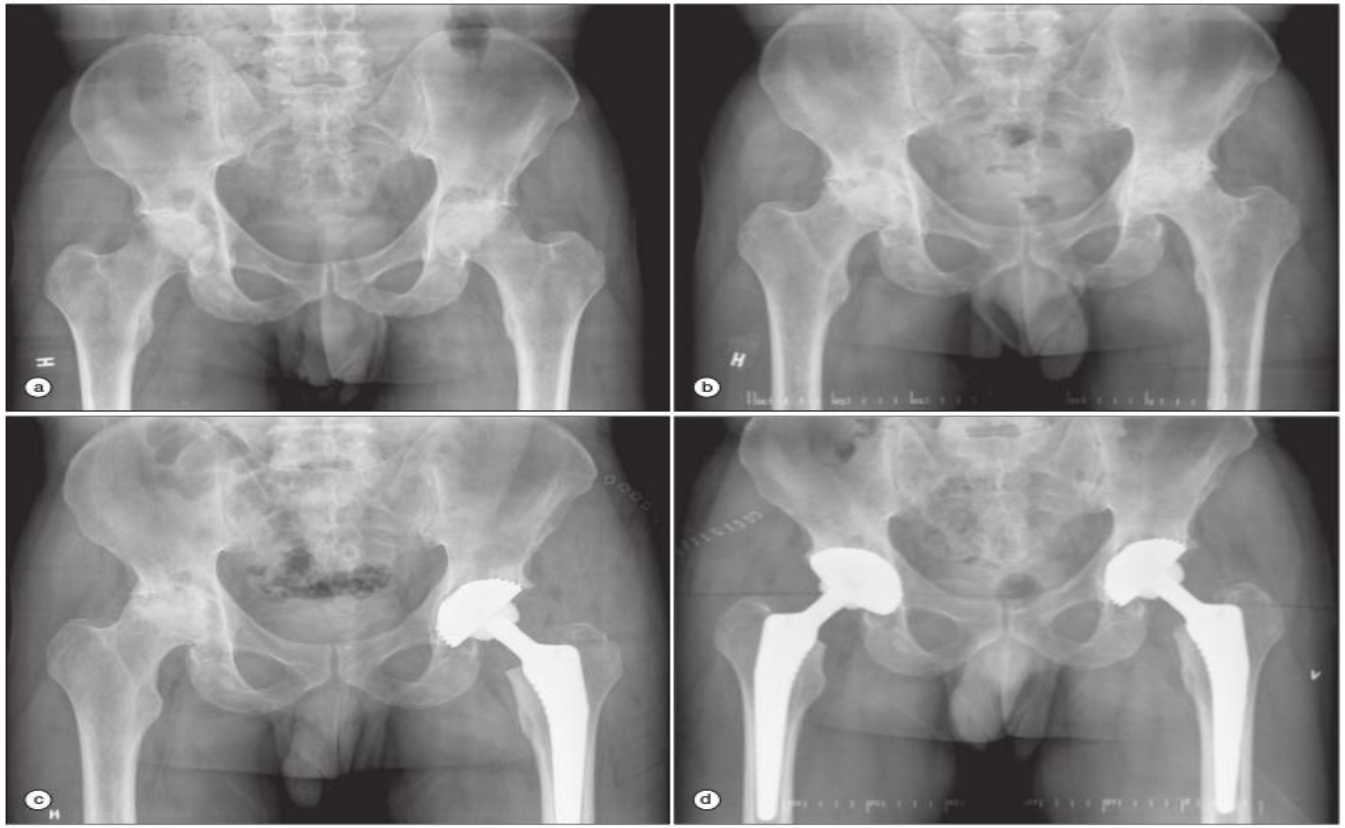
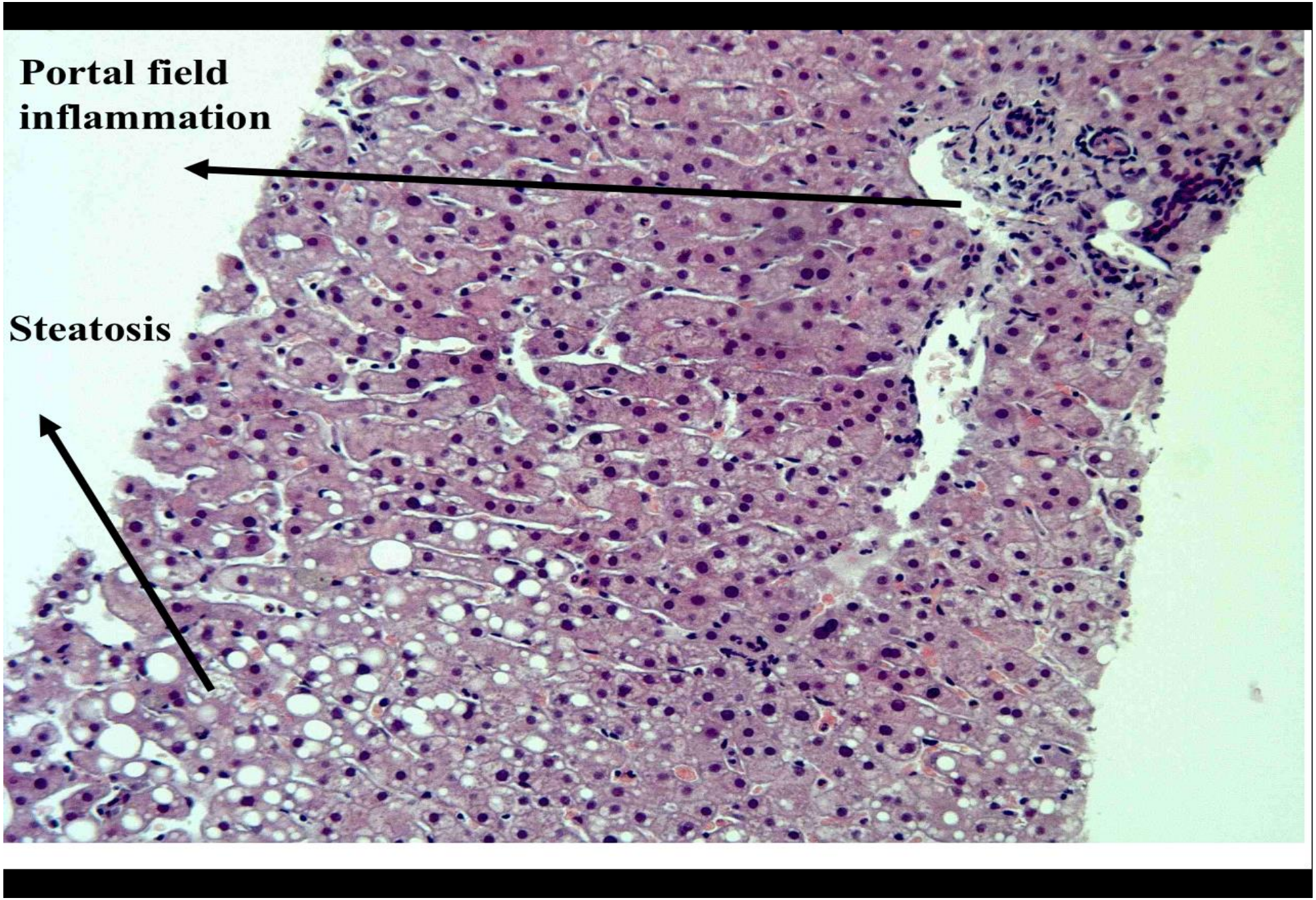


Fig. 84.7 Root joint involvement in AOSD in a 42-year-old man. Erosive disease evolved rapidly in both hips (a to d) and the left shoulder (e to g) despite aggressive cytotoxic therapy.

relates primarily to the development of articular complications because most internal organ complications remit with treatment.[5,31,75] Early studies have drawn particular attention to the development of carpal abnormalities as a diagnostic tool for AOSD because pericapitate abnormalities without radiocarpal alterations were more frequent in AOSD than in RA.[3,76] In these studies, carpal ankylosis developed after 1.5 to 3.5 years of disease with progressive joint space narrowing and

patients after 5 years of disease.[22] The main articular damage associated with poor functional outcome is, however, due to rapidly progressive erosive joint disease in root joints (Fig. 84.7); early risk factors for joint damage include the presence of polyarthritis with shoulder and hip involvement, increased ferritin levels, and increasing ferritin/CRP ratios.[13,31,48,51,58] It would be reasonable to manage such patients in a more aggressive manner in an effort to prevent damage development


Portal field inflammation
Steatosis

BAOJ Allergy & Immunology

Naohito Ohno, et al., BAOJ Aller Immunol 2016, 2: 1
2: 006

Research Article

The Challenges in the Diagnosis and Treatment of Still's Disease

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Abstract

Adult onset Still's disease (AOSD) is a rare disease in adults, in children also known as systemic juvenile idiopathic arthritis. We describe two patients with intermittent fevers without unknown origin. 27 years man and 75 years old woman, who presented with lymphadenopathy and recurrent fevers, There has been used intensive serologic, radiologic, laboratory investigation to exclude infectious diseases and malignancy. All the investigation showed no diagnosis. The clinical disease described for the first time at 1897 by Dr Still is finally diagnosed. Both patients received Anakinra with rapid response in hematologic, biochemical, and cytokine markers with reduction of systemic and local inflammation.

Keywords: Systemic JIA; Juvenile Idiopathic Arthritis; Remitting Fever; Autoimmune; Macular or Maculopapular Exanthema; Low-Grade Persistent Fevers; Biological; IL-1B Antagonist, Still's Disease

Introduction

Adult-onset still's disease (AOSD)

AOSD is a rare systemic inflammatory disease of unknown etiologic that often presents as a fever of unknown origin. Systemic features, such as spiking fever, skin rash, generalized lymphadenopathy, hepatomegaly, splenomegaly, and serositis, was first described by the British paediatrician George F. Still in 1896 [1] and by Bywaters in 14 patients in 1970 [2]. The aetiology of AOSD still remains unknown, but over expression of Th1 cytokines and IL-1 may have a critical role [3]. Pericarditis, pleural effusions, and severe abdominal pain may be present and confound diagnosis [4].

Daily fevers, evanescent rash, arthritis, hyperferritinemia, and liver dysfunction were consistent with AOSD [5-7]. Hyperferritinemia has a high sensitivity for AOSD (80%) but has a low specificity (40%) [8]. the fraction of glycosylated ferritin is higher than with inflammatory conditions. The combination of elevated serum ferritin level and low (20%) fraction of glycosylated ferritin can make the diagnosis of AOSD most likely [6]. In fact AOSD has similarities to auto inflammatory diseases, as exemplified by a central role of the innate immune system and by the cytokines involved (e.g., interleukin-1B [IL-1B]) [10,11]. Moreover, the blocking of both IL-1B has been shown to be efficacious in the treatment of AOSD [12,13]. Anakinra, IL-1B receptor antagonist, has been studied in AOSD, with favorable results [14,15]. AOSD patients had significant improvement with anakinra. In a study by Pascual and coworkers, seven of nine patients with AOSD had an excellent response to IL-1B inhibition [16].

Case Reports

Case 1

A 27-year-old Caucasian male presented at his first admission with an episode of fever since 4 weeks, diffuse myalgia, soar throat, cold chills and fatigue. The patient was in his usual state of health until 1 month before admission, when he developed fever. He had an 18-pound weight loss over the preceding month. During the fever attacks he had fatigue. The patient's medical history was unremarkable except an episode of fever after a streptococcal infection ten years ago. There was no family history of autoimmune diseases. He was on low dose Diclofenac as medication upon admission.

Physical examination showed normal vital signs with fever of 40.0° Celsius (104° F). The remainder of the physical examination was unremarkable.

Laboratory test revealed elevated inflammatory markers, including erythrocyte sedimentation rate (ESR; 116 mm/hour), C-reactive protein level (266mg/litter). A peripheral leucocytosis was present, with a white blood cell count of 22 000/mm3 (normal range 4,500–11,000). WBCs, 90 % neutrophils. The serum ferritin level was markedly increased at 5696 ng/ml (normal range 10–200). Urine cultures showed no infection and proteinuria was absent. An infectious disease evaluation was performed and was negative. Serologic study of Rheumatoid factor and anti nuclear antibody was negative. Antibodies to Sm/RNP, Ro/SSA, and La/SSB; anti cardiolipin antibodies; ant neutrophil cytoplasmic antibodies (ANCAs); and anti–cyclic citrullinated peptide antibodies were negative, and creatinine phosphokinase was normal. A chest radiograph was normal. Transoesophageal echocardiogram was performed by cardiologist the next day and ruled out endocarditic. (No vegetation's, some pericardial fluid).

After being well during 1 year after hospital discharge he complained

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of since 1 month existing fatigue, diarrhoea, nausea, vomiting, with fever up to 40.3° Celsius (104.54° F). He had recognized dark urine and light coloured defecations. Physical examination at his second admission showed a sick patient with dry mucosa. Blood pressure 123/55, icteric skin, decreased skin turgor. Submandibular, right lateral sternocleidomastoid and right groin lymphadenopathy, all noduli seemed benign. Temperature was 38.9° degrees Celsius (102° F), the pulse rate was 122 beats/ minute, and the respiratory rate was 12 breaths/minute. Abdomen is extended with normal with normal bowel sounds, splenomegaly and hepatomegaly 10 cm below the costal arch. His liver function deteriorated and clotting indices were also deranged.

Liver biopsy showed no specific inflammation. See Image 1. Prednisone 60 mg/day was started. The patient's localized rash and fever resolved spontaneously. Liver function showed improvement. He was discharged from our hospital after 3 weeks.

Case 2

75 years old women presented at our hospital with since months daily fevers between 38 to 39.5° Celsius (100.4°-103.1° F) with night sweats. Her complaints were of fatigue, dizziness and nausea. Besides the febrile episode she felt well. Attacks of fever occurred sometimes 2 times a day and reached normal level. She lost 10 kilograms in 1 month. There was no family history of autoimmune disease. She had Diabetes Mellitus type II, atrium fibrillation in medical history and used atenolol/chlortalidon 1dd100/25 mg, Metformin 2dd500 mg.

Physical examination revealed fully alert, oriented, and lucid sick women. Her vitals sign were as follows. Blood pressure 150/80 mm Hg. Heart beat 76/minute, her oxygen saturation was 95% on room air, and Temperature 37.8° Celsius (100° F), her respiratory rate was 18 breaths/minute unlaboured. Unilateral right sided supraclavicular lymphadenopathy with right thyroid gland nodule. Examination of her heart revealed an irregular tachycardia (atrial flutter on ECG) but no murmurs, rubs, or gallops. The lungs were clear to auscultation. There was no evidence of hepatosplenomegaly, skin rash, focal motor weakness, sensory deficits or arthritis. Laboratory examination showed elevated inflammation levels (CRP 133 mg/L, BSE 48 mm/h). Leucocytes 13.1/nL Neutrophils 11/nL . Calcitonin lightly elevated. No M protein detectable, ACE not elevated. Assays for antinuclear antibodies, antibodies to double stranded DNA, rheumatoid factor, anti-neutrophil cytoplasmic antibodies, anti-phospholipid antibodies, and cryo globulins were negative. The serum C3 and C4 levels were normal. A serum protein electrophoresis test showed normal levels of all immunoglobulin and no monoclonal spike. Blood cultures and a tuberculin test were negative. ECG: Atrium flutter. A complete work-up, including lymph node, bone marrow biopsy, was done to exclude malignancy. Her blood, stool, urine cultures and viral serology were all negative. All serologic examination was negative. Chest radiogram showed cardiomegaly. An ultrasound scan of the abdomen showed no abnormalities. CT thorax showed multiple pathologic mediastinal lymphomas (Figure 2).

Pet scan revealed elevated uptake of contrast (iodinated intravenous barium) in multiple pathologic nodules, high supraclavicular right and meditational (Figure 3). Mediastinal lymph nodule biopsy showed no malignant cells, only non-specific reactive Para cortical hyperplasia. Cytological punction thyroid gland nodule was normal. Bronchoscopy revealed normal lower airways.

During Hospital admission of 7 weeks, she had daily fever attacks with hypotension during febrile episode and 2 periods of 4-5 days without fever. Most of the febrile attacks occurred at night or early

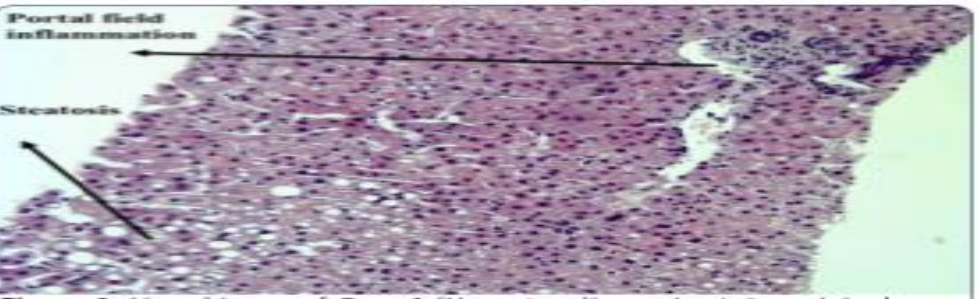


Figure 1. Liver biopsy of Case 1 (Hematoxylin-eosin stain, original magnification 400x)

Pathology report: Chronic non specific hepatitis , no necrosis and only slight inflammation at portal field . The biopsy of the liver and lymph nodule biopsy showed no typical sign of malignancy, tuberculosis infection, other infectious cause, sarcoidosis or Kikuchi disease. The only finding at histological examination was nonspecific reactive para cortical hyperplasia.

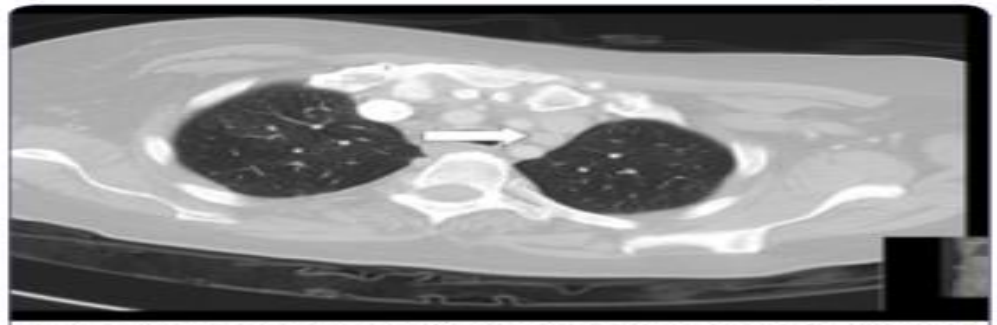


Figure 2: Figure 2 Patient B Ct thorax: multiple lymph nodules increased in size

Gantry 0 degrees, FoV: 312 mm, Time 500 ms, Slice 5 mm, 486 mA, 120 kV 14th slice from 75

	Cush et al (1987)*	Yamaguchi et al (1992)*	Fautrel et al (2002)*
Design	Single center, retrospective	Multicenter, retrospective	Single center, retrospective
Data analysis	Descriptive	Discriminatory statistical analysis	Logistic regression analysis
Cohort size	21	90	72
Disease duration	11.8 years	3.8 years	2.9 years
Case definition	Fever ≥ 39°C and arthralgia/arthritis with any 2 of: leukocytosis, JRA, rash, serositis/RES involvement	Clinical diagnosis upheld after case review by expert committee	Patients undergoing ferritin measurement and clinical diagnosis upheld after prolonged observation and case review by one expert
Excluded from analysis	RF > 1:80 ANA > 1:100	Non-definite cases after review (n = 56)	Non-definite cases after review
Comparator group	None	267 definite non-AOSD cases	130 definite non-AOSD cases
Criteria set	Fever ≥ 39°C and arthralgia/arthritis with any 2 of: leukocytosis, JRA, rash, serositis/RES involvement	Major: Fever ≥ 39°C for > 1 week, arthralgia > 2 weeks, maculopapular non-pruritic salmon-pink rash, leukocytosis ≥ 10,000/mm³ with ≥ 80% neutrophils Minor: Pharyngitis or sore throat, lymphadenopathy, and/or splenomegaly, abnormal aminotransferases, negative rheumatoid factor or ANA assay	Major: Spiking fever ≥ 39°C, arthralgia, transient erythema, pharyngitis, neutrophils > 80%, glycosylated ferritin fraction < 20% Minor: Typical rash, leukocytosis ≥ 10,000/mm³
Required	As above	At least 5 criteria, including 2 major	Four major criteria or 3 major and 2 minor criteria
Exclusion needed	None	Infections, malignancies, vasculitides	None
Sensitivity for set	Not analyzed	96%	81%
Specificity for set	Not analyzed	92%	98%

JRA, juvenile rheumatoid arthritis; RES, reticuloendothelial system; RF, rheumatoid factor; ANA, antinuclear antibody.

Diagnostic criteria for AOSD

References in table		Reference number	Name of criteria	
		6	Yamaguchi et al (1992)	
		7	Fautrel et al (2002)	

Note: criteria sets proposed to assist in distinguishing aosd patients

IL-1 inhibitors have been reported to be markedly effective in the management of systemic-onset juvenile idiopathic arthritis, adult-onset Still disease [11]. For the evidence that exists of the use of antagonists of IL-1B in the literature [12-16].

In case 1 the first 7 years after onset of AOSD corticosteroids and at fourth year from onset of AOSD is modifying anti rheumatoid drug (DMARD) Methotrexate (MTX) added with good response. Only after years and two severe relapses of AOSD by an unresponsive disease course treatment with DMARD MTX and corticosteroid is switched to biological IL-1B antagonist. Two months after start systemic inflammation and fever attacks improved. The liver function and inflammatory parameters are normalized.

Case 2 did not receive corticosteroids as first choice because of presence of dysregulated diabetes mellitus type II. The use of corticosteroids has an unavoidable side effect on blood glucose levels on patients with Diabetes Mellitus that is dysregulated due to AOSD episode.

She had a 2 months long admission with multiple investigations without proper treatment. To shorten her quality of life as soon as possible, at second month of admission is the treatment with IL-1B antagonist started. Methotrexate is relatively slow acting drug (response starts weeks after first intake) compared with IL-1B antagonist. The response to IL-1B inhibitors is very rapid compared with MTX and occurs within days and sometimes a few hours after the initiation of therapy. In other patients especially children and young adults, the first choice of treatment remains corticosteroids and DMARDs [17,18,22].

The feasibility of IL-1B antagonist is limited by the fact that it is currently available only as a daily subcutaneous injection that causes significant burning and pain. This pain is caused by allergic reaction (mast cell degranulation) after administration of the vehicle constituents in combination with a relatively large amount of anakinra in a highly concentrated protein [23]. Another side effect or toxic effect of IL-1B antagonist is that it can cause neutropenia and serious infections if it is concurrent administered with biological Enbrel(TNF inhibitor). Patients who already have neutropenia should not start with IL 1B antagonists. Only 2 % of adult patients that started with IL-1B antagonist had a decrease in neutrophil count but no neutropenia.

In Children there are more adverse effects of IL-1B antagonists

reported. The major adverse effects of anti-IL-1 therapy include injection site reaction (anakinra; rilonacept; canakinumab) and infections, particularly gram-positive (especially pneumococcal) infections [24]. Up-to-date vaccina tions, including pneumococcal vaccination, should be ensured in children receiving anti-IL-1 therapy.

Macrophage activation syndrome (MAS) could be the initial form of AOSD [36]. However appearance of this complication during diagnostic process or evolution of disease is most common. It is even possible to have an induction of MAS by children treated with IL-1B antagonists. Macrophage activation syndrome has severe consequences if left untreated (cytopenia, hypertriglyceridemia). Bone marrow aspiration and biopsy is needed for diagnosis of MAS. Treatment of MAS consists of pulse corticosteroids methylprednisolon intravenous, intravenous immune globulins, cyclosporine.

MAS can be a complication of treatment with anti IL1B antagonists in children. MAS can also a form of AOSD which needs to be treated with IL1B antagonists.

Autologous stem cell transplantation (ASCT) can be an option for treatment of AOSD and for children with systemic onset juvenile idiopathic arthritis (childhood form of AOSD). Still a big price for a therapy induced complication.....

Final Diagnosis

Adult Onset Still's Disease

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