CASE REPORT

# Thirty two years old patient with adult Still's disease

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**Abstract**

**Adult Still's disease is characterized by diverse clinical and laboratory findings, which may lead to errors in the differential diagnosis, and possible injury of the patient's health due to wrong therapeutic management.**
**In the following case report, we describe a case of a 32-year old patient with fever of unknown etiology. The final diagnosis of Morbus Still adultorum was determined five months after his first check-up. The course of the disease was complicated by acute hepatitis caused by drug toxic damage. We have applied immunosupressive therapy with very good clinical and laboratory responses.** ***(Ref. 9.)***
**Key words: Still's disease, fever of unknown etiology.**

We reported case report of 32 years old patient who has been rehospitalized in District general hospital (DGH) due to fever lasted for two months. Then he has been transmitted to the Institute of Preventive and Clinical Medicine (IPCM) at the Department of Clinical Immunology and Pharmacotherapy to specify (to establish) the diagnosis.

History of the patient's troubles has been started on May 2000, when he has been examined by general practitioner. Fever up to 40 °C, weekness and sore throat were the dominated symptoms in clinical picture. The general practitioner decided to aplicate antibiotic drug (ATB) Penebene, penicillins, which has been during several days excluded because of the manifestation the skin allergy (pruritic skin exantem). The treatment has been continued by the administration of macrolides ATB (Summamed). The efficacy of ATB therapy has not been succesfull and due to persistence of fever the patient has been admitted to the Department of Infectious diseases of DGH. Fever up to 40 °C weakness, artralgia and myalgia were dominated symptoms in patient troubles. Joints such as knees and the small joints of hands were affected mostly. Personal history was negative except the trauma of knee joint that happend several years ago during the skiing. Allergy history was positive (above mentioned skin allergy caused by Penebene). He worked as a stores attendant and with toxic substances he had no any contact. Beeing non-smoker, alcocohol abuse 1—2 beers daily. Physical examination revealed hepatosplenomegaly, enlarged solitar lymphatic node in right illiac region. The sonography confirmed the hepatosplenomegaly. Laboratory tests showed following inflammatory signs: high sedimentation rate (FW 80/105), positivity of C-reactive protein (CRP μg/ml), leukocytosis with neutrophilia in leukogram (Leu $16.5x10^9$/l, leukogram: neutrophils 74 %, eosinophils (Eo) 2 %, monocytes 2 %, lymphocytes 22 %), mild anaemia (eyrthrocytes $3.44x10^{12}$/l, hemoglobin 124 g/l, hematocrit 35 %, plateles $330x10^9$/l). Biochemical parameters showed on the elevation of liver function tests (5 times upper physiologic range) with cholestatic feature (AST 2.8 μkat/l, ALT 4.28 μkat/l, GGT 8.8 μkat/l, ALP 10.4 μkat/l). The values of bilirubin were in reference range and mild hypoalbuminaemia (34.6 g/l) has been observed, urine analysis negative. The microbial examination excluded the infectious origin of fever (negative tampon of tonsils, ASLO, anti-HIV, RRR, HBsAg, anti-HBs, anti-HCV, antibodies against leptospirosis, tularemia, chlamydia, yersinia, toxoplasmosis). Due to persistence of fever and positive microbial test from haemoculture (Staphylococcus epidermidis) the cephalosporines of third generation (Linesolid, Azitormycin, Astreonam), antimycotic drug (Fluconazol) and antipyretic drug (Paralen) have been administered. Despite this chemotherapy the clinical picture have not improved and the fever persisted. Next step was to consult

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fully trained specialist in a branch of rheumatology with following conclusion: fever of unknown ethiology with reactive arthritis and recommended administration of corticosteroids (Hydrocortison 300 mg parenteraly devided into 2 doses). After administration of indicated therapy the drop of fever and improvement of clinical status has been seen. The patient has been discharged to home care. One month later the patient has been admitted once again at the Department of Internal Medicine of DGH, due to elevation of fever. Basal laboratory tests have not been different from those obtained at preceding stay at the Department of the Infectious Diseases. Infectious origin of fever has been again excluded. Hepatoslenomegaly and enlargement of solitary lymphatic node in illiac region has been confirmed. Due to suspicion on lymphoproliferative disease histologic examination of bone marrow has been done, but did not excluded definitely lymphoproliferative process due to findings of mild fibrosis in mostly of marrow spaces. The patient has been discharged to home care in short time and the therapy with antipyretic drug (Paralen) has been recommended. Two days later rapid worsen of clinical status due to developement of acute hepatitis has been observed. Infectious origin of hepatitis by serologic tests has been excluded, but its did not correlated with histologic findings of liver biopsy. Inflammatory changes presented in histologic picture did not excluded chronic viral hepatitis. Then pulse therapy with corticosteroids (Methylprednisolon) in doses 1 g per day during 3 day has been administered. Several days later at the onset of July 2000 year the patient was transported to the ICPM at the Department of Clinical Immunology and Pharmacotherapy in Bratislava.

Fever up to 40 °C, weakness and artralgia have been dominated symptoms. In laboratory tests signs of acute hepatitis with elevation of liver function tests (transaminases above to 30 times of upper reference range) with cholestatic feature (AST 29.5 μkat/l, ALT 33.0 μkat/l, GGT 7.34 μkat/l, ALP 6.29 μkat/l) with gradually progress of hyperbilirubinemia (Bilirubin total 356 μmol/l, Bi conjugated 267 μmol/l) have been noticed. Urobilinogen has been positive in urine analysis. Disorder of proteosyntetic function of liver (hypoalbuminemia) has been seen (albumin 27.12 g/l), drop of coagulation function (Quick's time 62.8 %, INR 1.39). Autoimmune origin of acute hepatitis has been excluded by negative tests of autoimmune phenomenons (ANA-antibodies (ab) against nuclear antigens (Ag), ASMA-ab against smooth muscles, ALKM-ab against microzomes of liver and kidney, AMA-ab against mitochondria, LSA — liver specific Ag). We have been provided tests to exclude viral origin of acute hepatitis. Ab against core Ag of virus hepatitis B has been assessed, but the assessment of HBV DNA by PCR method excluded the replication of virus.

Following immunologic parameters, both cellular and humoral immunity, have been assessed. In cellular immunity leukocytosis (Leu 14x10/l), with physiologic ratio of neutrophils and lymphocytes, but with eosinophilia (Eo 7 %), decreased phagocytosis (activity of phagocytosis 58 %), increased relative count of CD3 positive T lymphocytes, of CD3 HLA DR positive and CD8 positive (subpopulation of supressor lymphocytes), with depression of immunoregulatory index (IRI) to 0.62 (IRI — reference range 0.86—2.72), have been noticed, respectively. In humoral parameters elevation of C3 component of complement, and increased activation of complement activated by alternative pathway, increased levels of CRP (28.04 μg/ml) and circulating immune complexes (54.92 units) have been assessed, respectively. The levels of immunoglobulins except of immunoglobulin class E (IgE total 1722.9 μg/l, reference value <240 μg/l) have been in reference range. In the skin test of delayed — type hypersensitivity anergy has been seen. Above reported immunologic findings confirmed atopic constitution of subject and the deficiency in both — natural and specific cellular immunity, with positive markers suggested acute inflammation. This must be important to notice, that examined immunologic status of patient has been modified by preceding incomplete, administration of immunosuppressive therapy (pulse coticosteroid therapy).

After completion of laboratory tests and detailed analysis of patient's history we have became to the conclusion, that contemporary acute injury of liver has been enhanced by preceding administration of hepatotoxic chemotherapy. Our suspicion to toxic injury of liver by drugs has been confirmed by reevaluation of histologic findings of liver biopsy. The hepatoprotective regime has been aplicated and potentially hepatoxic drugs (antipyretic drug — Paralen) have been excluded from the therapy. After these measures laboratory tests gradually lowered to physiologic range and clinical status rapidly improved. The patient without manifestation of fever has been discharged to home care with the diagnostic conclusion of acute hepatitis caused by toxic drug administration. The continuation of hepatoprotective regim including administration of hepatoprotective drugs (Flavobion, Lipovitan) has been recommended.

Three months later the patient has been again admitted to the Department of Clinical Immunology and Pharmacotherapy with the similiar troubles: fever (40 °C), the pain of small joints of both hands, knees accompanied with mild oedema without evident signs of acute inflammation. Sonography confirmed hepatosplenomegaly. Laboratory tests revealed positivity of inflammation signs, mild hypochromic anaemia, hyposideremia and elevation of ferritin levels (ferritin 1731 ng/ml, reference range 15—232 ng/ml), hypoalbuminemia, elevation of transaminases (above 2-times of upper reference values). Tests of autoimmune phenomenons have been negative (rheumatoid factor, ANA). Wee have indicated a rebiopsy of bone marrow, because the previous histologic finding has not been definite. The indicated biopsy has been done without the precedented administration of the corticosteroids, which could change histologic picture. Conclusion of histologic findings confirmed, but not specify, the kind of autoimmune disease.

The final diagnosis of adult Still's disease has been based on analysis of patient's history, clinical picture and laboratory tests. The course of disease has been complicated by secondary drug liver injury. We have immediately started immunosupresive therapy with Prednison in dose 1 mg/kg/day during 6 weeks. The benefit of immunosupression has been manifestated already af-

ter several days. The patient has been discharged to home care afebrile with reference values of laboratory findings.

**Discussion**

Adult Still's disease is predominantly kind of disorder of young adults aged 16—35 years (Esdaile, 1981). This rare disease is found wordwilde.

In our case report we described complicated diagnostic approach from the suspicion on septicaemia, myeloproliferative disorder to the establishment of final diagnosis adult Still's disease, which has been complicated by the drug toxic liver injury. It is important to stress, that the clinical course of disease has been affected by intermittent, incomplete immunosuppressive therapy. It is important also to mention that the full constellation of clinical features may be not present at onset and that evolution to a typical case of adult of Still's disease may take a number of weeks, rarely even months. This disease commonly presents with a high fever (39 °C) in 97 % of cases, artralgia (100 %), sore throat (92 %) and rash (mucocutaneus lesions, 88 %), myalgia (84 %) (Esdaile, 1994). In our case report the onset of disease has been similiar (fever, sore throat, artralgia and myalgia). In reported patient the typical rash for adult Still's disease could be modified by intermittent corticoid therapy and by the development of severe icterus.

The laboratory test results largely reflect the systemic inflammatory nature of the disease. An elevated sedimentation rate is universal. The platelet count is high in over 50 % of patients and hypoalbuminemia is present in 81 %. Sixty-eight percent have a significant anaemia. The most striking abnormality is a marked leukocytosis. Over 75 % of patients have a peripheral white blood cell count >15x10/l. The increase in cells is predominantly due to an increase of mature and juvenile neutrophils. Recent reports have noted a striking elevation of serum ferritin in patients with adult Still's disease in comparison to other inflammatory disorder (Ohta et al., 1990; Yamagouchi et al., 1992).

Tests for rheumatoid factor, antinuclear antibodies and other autoantibodies are generally negative. Occasionally positive tests (rheumatoid factor 1 %, and ANA antibodies 6 %) are seen in low — titer and generally transient. All laboratory results were also seen in our patient.

Elevation of one or more liver function tests, particularly transaminases is seen in two third of patients (Esdaile et al., 1979; Esdaile et al., 1994). In our patient the clinical course of the disease has been complicated with administration of hepatotoxic drugs especially antiinflammatory agents (ATB, antimycotic and antipyretic drugs), which led to the development of acute hepatitis. Positivity of liver function tests may be characteristic feature of laboratory findings of adult Still's disease and in our case liver injury has been enhanced by the administration of hepatotoxic ATB (Azitromycin, Aztreonam, Linezolid), antimycotic drug (Fluconazol) and antpyretic drug (Paralen) (Micromedex, 2001 a, b, c, d).

In the process of differential diagnosis we had the suspicion of viral liver injury based on the positivity of liver histology and positivity of antibodies against core Ag of virus hapatitis B. The assessment of HBV DNA by PCR method definitely excluded the replication of virus. It is important to note that interpretation of serologic parameters could not be definite, especially in the group of rheumatologic diseases. Positive false reaction can be seen in these diseases and this phenomen could not be excluded also in case of our patient.

Abdominal pain has not be presented in our patient, but were reported cases with wrong surgical intervention (Esdaile, 1994).

The treatment of adult Still's disease requires intensive immunosuppressive therapy. Optimal is corticosteroid pulse therapy (methylprednisolon in dose of 1 g/daily during 3 days) and follow up with peroral formula (Esdaile, 1994).

In conclusion — it is important to note that physicians (general practitioners) in cases of unknown etiology of fever must keep in mind also the existence of adult Still's disease. The diagnosis must be based on detailed analysis of patient's history, physical examination and laboratory tests.

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