ADULT ONSET STILL'S DISEASE PRESENTING WITH FEVER OF UNKNOWN ORIGIN

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Adult onset Still's disease is a rare systemic inflammatory disorder of unknown etiology, characterized by spiking fevers with an evanescent rash, arthritis, and multiple organ involvement. Adult onset Still's disease is also one of the most frequent etiologies of fever of unknown origins (FUO). This 23-year-old male patient presented to our hospital with a chief complaint of daily fevers off and on for 4 weeks. A rash over his legs and arms developed, especially during the fever. Also, left knee and right shoulder joint pain was noted. Infective endocarditis was ruled out by negative echocardiography, negative blood culture result and no new onset murmur. Due to the quotitian fever with rash and arthralgia, adult onset Still' disease was diagnosed. After prednisolone and other immunosuppressive agents were given, the fever and arthralgia subsided promptly. Clinical resolution was achieved and laboratory markers (such as the ferritin and leucocyte count) dropped. He was followed up at the outpatient clinic with clinical remission.

Key words: **adult onset , Still's disease, fever of unknown origin (FUO).**

Adult onset Still's disease is a rare systemic inflammatory disorder of unknown etiology, and is characterized by quotidian or double-quotidian spiking fevers with an evanescent rash, arthritis, and multiple organ involvement. After the first description by Bywaters in 1971[1], increasing numbers of patients with adult onset Still's disease have been reported, but the diagnosis of adult onset Still's disease is difficult and often delayed because of the vague and nonspecific clinical pictures. Due to the difficulty of diagnosis, those patients often suffered from prolonged fever. Adult onset Still's disease is one of the most frequent etiologies of fever of unknown origin (FUO). We hereby report a case with prolonged spiking fever who was finally diagnosed as having adult onset Still's disease and was successfully treated with immunosuppressive agents.

CASE REPORT

This 23-year-old male came to our hospital complaining of daily fever off and on for 4 weeks. He was healthy until Sep. 23, 2004. Fever, productive cough, urine frequency and burning sensations had developed. He was sent to our Emergency

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Department on Sep. 29, where laboratory data showed: WBC 20,841/ul (segment 82%), CRP 26.7 mg/l. Chest X ray, urinalysis and blood culture revealed negative findings. Then, he was admitted to a University Hospital from Oct. 6 to 18, but was discharged without definite diagnosis. He came to our Emergency Department again on Oct. 31 due to fever, laboratory data showed WBC: 24,721/ul (Segment: 91%) ,CRP: 21.01mg/l. However, no evidence of pneumonia, or abnormal urinalysis was noted. He was admitted to our medical ward under the impression of FUO. He denied any systemic disease history. He was previously addicted to amphetamines but had been free of this addiction for 5 years. He denied recent travel or unusual exposure.

Physical examination revealed a thin man who was ill looking, blood pressure: 140/70 mmHg ; P.R:123 /min ; R.R:16 /min. Fever pattern is one to two spiking fever up to and above 39°C and return to normal temperature in the same day. His consciousness was clear with intact skin and no abnormality of the head, eye, ear, nose and throat. Parenteral antibiotics with cefazolin 1 g q8h and gentamicin 100 mg intravenous drip qd were given since admission under the impression of FUO. Antibiotics were changed to crystal penicillin 3MU intravenous stat and q4h and Levofloxacin 1 g intravenous drip stat and 500mg intravenous drip qd. Infective mycotic aneurysm, intra-abdominal infection was suspected owing to a grade III abdominal aortic bruit over the mid-abdomen, grade I-II pansystolic murmur over left lower sternal border and apex. However, no new onset murmur and adequate left ventricular function, nor evidence of endocarditis were shown by the echocardiogram and physical examination. During the disease course, more than 7 sets of blood culture were obtained with negative results.

During admission, the rash developed especially when temperature spikes were noted. The skin rash was salmon pink in color, covering the bilateral inguinal area and leg. Left knee and right shoulder joint pain were also complained of.

Tumor markers of AFP and CEA were within normal limits. Bone marrow showed normal cellularity and neither granuloma nor malignancy was found. The titer of antinuclear antibody (ANA) was 1:40 (-), Rheumatoid factor (RF) was below 20 IU/ml, C3: 187.9 mg/dl (90-180), C4: 36.8 mg/dl (10-40), anti-HIV antibody (-), VDRL (-), HLA B27 (-), ferritin 1560.88 ng/ml and no monoclonal gammopathy was also noted.

Due to the quotitian fever with rash and arthralgia, adult onset Still's disease was suspected. Intravenous solucortef 100 mg once was administered with prompt resolution of fever, arthritis, and rash. Recurrent fever with the body temperature rising to 38.1°C occurred once 2 days later, but returned to normal and remained afebrile afterwards. Prednisolone 10 mg twice a day and plaquenil 200 mg twice a day was given. His clinical condition improved and was discharged. Presently, he is in clinical remission with medications of metho-

Table 1. Laboratory findings of this patient.

date	WBC/ul	Seg %	CRP mg/dl	Hgb m/dl	Ferritin ng/ml	ESRmm/hr 30'/60'	GOT/GPT U/L
940929	20841	82	26.07	14.4			37/36
941031	24721	91	21.1	10.2			
941102	20561	89		8.9			
941108	16191	81		9.3	1560.88		25/74
950419	13050			13.3	353.73	11/50	

trexate 7.5 mg per week, and prednisone 7.5mg twice daily. Laboratory tests showed that WBC has decreased to 13,050/ul, and ferritin to 353.73 ng/ml (Table 1).

DISCUSSION

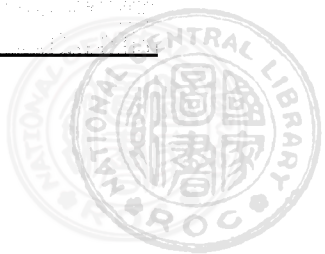
Adult onset Still's disease typically manifests as a triad of symptoms that include high-spiking fever, a characteristic rash, and arthritis/arthralgias.[2] According to Yamaguchi's criteria [3], this patient fulfilled all four major criteria (arthralgia, fever, typical rash, leukocytosis) and three of four minor criteria (sore throat, abnormal liver function test, negative ANA and RF) (Table 2). There was no evidence of septic picture, no positive blood culture results, no elevation of tumor markers value, negative bone marrow biopsy and no evidence of other rheumatic disease in this patient.

Schnitzler syndrome is defined as a unique constellation of clinical and biologic signs including chronic urticaria, intermittent fever, bone pain, arthralgia or arthritis, and a monoclonal IgM gammopathy [4]. Both adult onset Still disease and Schnitzler syndrome share the symptoms of skin rash, fever, palpable lymph nodes, spleen and liver enlargement, arthralgia, and leukocytosis [5]. However, ferritin levels are usually more elevated in the former while a monoclonal IgM component is present in the latter. In this patient, ferritin levels were high, rash was evanescent, subsiding after fever and disappearing after treatment, peripheral blood smear and bone marrow findings were negative, and there were no monoclonal gammopathy or other abnormal hematological findings.

The definition of FUO requires a fever higher

Table 2. Adult onset Still's disease, the diagnostic criteria of Yamaguchi and this case's presentation

diagnostic criteria, Yamaguchi et all1	In this case
Major	
Arthralgia > 2 weeks	Yes
Fever > 39, intermittent more than 1 week	Yes
Typical rash	Yes
WBC > 10 000 (> 80% granulocytes)	Yes
Minor	
Sore throat	Yes
Lymphadenopathy and/or splenomegaly	No
Liver function test abnormal	Yes
Negative ANA and RF	Yes
Exclusion criteria	
Infections	Blood culture negative
Malignancies	AFP, CEA level within normal, no other evidence of malignancy Bone marrow biopsy negative
Rheumatic diseases	No evidence of other rheumatic disease
Diagnosis	
5 criteria (at least 2 major)	4 majors + 3 minors= 7 criteria



than 38.3°C on several occasions, persisting without diagnosis for at least 3 weeks in spite of at least 1 week's investigation in the hospital [6]. The main etiologic categories of FUO are infections, neoplasms, connective tissue diseases, miscellaneous diseases, and not being able to be accurately diagnosed. In a study of 130 patients with FUO, 36 (28%) had collagen vascular diseases. Of these 36 patients, 20 (56%) had adult onset Still's disease [7]. Due to the difficulty of diagnosis, the patient suffered from fever for around 4 weeks, since Sep 29, 2004, the first visit to our emergency room, to Oct 31, his 2nd visit.

Because the disease has heterogeneous clinical findings, certain bacterial infections (e.g. streptococcal pharyngitis and sepsis) are generally considered and the prescribing of antibiotics is common, as with our patient. In one study, antibiotics were prescribed in 18 (90%) of adult onset Still's disease cases. The presumed infectious diagnoses were streptococcal tonsillitis/pharyngitis (50%), infective endocarditis, sepsis and acute bacterial meningitis [7]. Infective endocarditis had been suspected in this patient, but the cardiac echo image didn't show any signs of vegetation, nor a new cardiac murmur or positive blood culture.

Markedly elevated serum ferritin concentrations were noted in around 70 percent of adult onset still disease patients [8]. This is probably due to an acute phase response, since inflammatory cytokines can increase ferritin synthesis [9]. Serum ferritin concentration correlates with disease activity, and was suggested as a serologic marker to monitor the response to treatment [10]. In this patient, the ferritin concentration was 1560.88 ng/ml prior to steroid treatment and dropped to 353.73 ng/ml in the Out Patient Clinic.

Treatment of adult onset Still's disease has been exclusively empirical, beginning with Bywaters in 1971[1], the use of NSAIDs, steroids, and antirheumatic agents are the mainstay of treatment. Masson, et al [11] demonstrated that 22/65 (34%) patients required additional remittive treatment to maintain disease control, 20 (91%) of whom were concomitantly receiving prednisone. In this case, intravenous solucortef 100 mg was given with prompt resolution of fever, arthritis, and rash. After prednisolone 10 mg twice daily and plaquenil 200 mg twice daily as maintenance therapy, his clinical picture improved.

In brief, adult onset Still's disease is a rare disease; it should be born in mind for the existence of FUO, after the exclusion of common autoimmune diseases and unusual infection.

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成人Still氏症以不明原因發燒來表現

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成人Still氏症是一種少見的全身性發炎性疾病，原因不明，特色是發燒伴隨有發疹，關節炎併發多器官表現。成人Still氏症常是不明原因發燒的可能原因之一。

一位23歲男性病人因為持續發燒四周而到本院求診，經急診入院，體溫會高達攝氏39度以上並在一天之內降回正常。住院時懷疑為感染性心內膜炎，但心臟超音波及血液培養結果皆為陰性，也沒有新的不明原因的心雜音出現。住院期間發現病患在發燒時合併有出疹現象，且這個病患同時有左膝和右肩關節痛。

因為發燒關節痛和出疹等現象，而懷疑是成人Still氏症。經過類固醇和其他免疫抑制劑治療後體溫迅速回復正常，其他臨床症狀改善和白血球和血清鐵素等數值也都下降，此病人繼續在門診追蹤。

關鍵字：成人Still氏症、不明原因發燒