

# Adult-onset Still's Disease in an Oriental Population: Manifestations, Course and Outcome in 16 Patients

E Lim,\**MBBS, M Med (Int Med)*, H H Chng,\*\**FAMS, MBBS, M Med (Int Med)*

## Abstract

*This retrospective descriptive study aims to characterise and compare the clinical manifestations, course and outcome of 16 Oriental patients with adult-onset Still's disease diagnosed in the last 4 years with published data based on Western populations and another Oriental (Japanese) series. Like the Japanese, we found a female preponderance, an older age at onset, and fewer patients with abdominal pain, myalgia, sore throat and serositis compared to the Western series. A longer delay in diagnosis occurred in patients lacking either arthritis or rash at presentation. Most patients had mild hyponatraemia and 2 patients had overt syndrome of inappropriate anti-diuretic hormone secretion. All patients showed a dissociation of elevated aldolase with normal to low creatine kinase levels. Over 50% relapsed within a year from diagnosis and needed slow-acting anti-rheumatic drugs as steroid-sparing agents. Two were given intravenous pulse cyclophosphamide therapy for progressive pneumonitis. Outcome was generally good with minimal functional impairment and no mortality.*

*Ann Acad Med Singapore 1998; 27:11-5*

**Key words:** Arthritis, Fever of unknown origin, Salmon rash, Urticaria

## Introduction

Although George Still first described systemic onset juvenile rheumatoid arthritis (JRA) comprising fever, arthritis, lymphadenopathy and splenomegaly in 1897, it was not until 1971 that its nosologic entity presenting in adulthood was recognised by Eric Bywaters.<sup>1</sup> Since then, well over 300 cases have been reported in the literature worldwide. Apart from a Japanese study, most data to date are from Caucasian populations. The aim of this study was to study the presenting features, clinical manifestations, disease course and outcome of adult-onset Still's disease in an Oriental population in Singapore and to compare these to published data.

## Materials and Methods

Clinical charts of 16 Oriental patients diagnosed from April 1993 to June 1997 with adult-onset Still's disease fulfilling the 1982 revised JRA criteria for Still's disease<sup>2</sup> were reviewed retrospectively. These patients were referred to the Department of Rheumatology and Immunology, Tan Tock Seng Hospital (the only tertiary referral centre for rheumatology in Singapore). The patients also included 3 foreigners of Oriental extraction.

## Results

### Epidemiology

Females outnumbered males 13 to 3. The racial distri-

bution was as follows: 11 Chinese, 1 Malay and 4 Indians. The mean age at onset was 35 years (range 18 to 67 years). Delay from onset until diagnosis averaged 3 months (range 0 to 12 months). The longest delays of 7 and 12 months respectively were in two patients who did not present with rash or arthritis at onset. No significant autoimmune association was noted, except for a patient with previous Graves' disease, and another with systemic lupus erythematosus (SLE), both of whom had remained in remission for over 10 years upon presentation of adult Still's disease, and did not have clinical or laboratory features to suggest a relapse of Graves' disease or SLE. Of interest is a patient with serologically proven and clinically consistent acute parvovirus B19 infection preceding Still's manifestation by 3 months, without evidence of persistent chronic viral infection such as positive parvovirus B19 IgM, leukopenia or thrombocytopenia.

### Clinical Features

All presented with spiking and remitting fever, accompanied by arthralgia in almost 90%. Other common presenting features included rash (63%), sore throat (50%) and cervical lymphadenopathy (25%). Only half of the patients had the classical triad of fever, arthralgia and rash at first presentation.

Table I shows the clinical manifestations eventually

\* Registrar

\*\* Senior Consultant

Department of Rheumatology and Immunology

Tan Tock Seng Hospital

Address for Reprints: Dr E Lim, Department of Rheumatology and Immunology, Tan Tock Seng Hospital, Moulmein Road, Singapore 308433.

TABLE I: CLINICAL MANIFESTATIONS OF 16 ORIENTAL PATIENTS

| Clinical Feature         | n  | %*  |
|--------------------------|----|-----|
| Fever                    | 16 | 100 |
| Athralgia                | 16 | 100 |
| Arthritis                | 13 | 81  |
| Rash                     | 13 | 81  |
| Sore throat              | 8  | 50  |
| Myalgia                  | 8  | 50  |
| Asthenia / weight loss   | 8  | 50  |
| Cervical lymphadenopathy | 8  | 50  |
| Hepatomegaly             | 6  | 38  |
| Splenomegaly             | 6  | 38  |
| Pneumonitis              | 4  | 25  |
| Pleuritis                | 2  | 13  |
| Abdominal pain           |    | 6   |
| Alopecia                 | 1  | 6   |
| Conjunctivitis           |    | 6   |

n = number of patients (out of 16) with the particular clinical feature

\* percentage of total i.e.  $n/16 \times 100$

evident on follow-up. The typical salmon-pink **enan-**them was seen in all but 2 of the 13 patients with rash. Six patients had pruritic urticaria, and 1 demonstrated Koebner's phenomenon. All but 1 had **polyarthralgia/**arthritis of a symmetrical distribution, involving mainly the small to medium-sized joints, and often associated with early morning stiffness.

### Investigations

Table II summarises some of the often extensive laboratory investigations undertaken to exclude infections, malignancies and the more common rheumatic diseases. The majority displayed neutrophilia, mild normochromic and normocytic anaemia, thrombocytosis, hypoalbuminaemia, hyperglobulinaemia, a mixed hepatic picture; and highly elevated erythrocyte sedimentation rates ( $63\% >100 \text{ mm/h}$ ), C-reactive protein ( $58\% >100 \text{ mg/L}$ ) and ferritin ( $50\% >1000 \mu\text{g/L}$ ) levels. A mild hyponatraemia was noted in the majority, and measured serum hypo-osmolality consistent with the syndrome of inappropriate anti-diuretic hormone (SIADH) secretion was documented in 2 patients. Of interest too was the universal elevation of serum aldolase with a normal to low creatine kinase level. The 2 patients with positive antinuclear antibodies did not have clinical features or autoantibodies suggestive of other rheumatic diseases. X-rays done did not show erosions or other joint damage.

### Management

Almost all received a non-steroidal anti-inflammatory drug (NSAID) as first-line treatment, except for 2 patients from whom it was withheld for fear of aggravating the hepatic dysfunction. Only 2 patients eventually did

TABLE II: LABORATORY TEST RESULTS AT FIRST PRESENTATION OF ILLNESS

| Test                                        | Mean  | Range      | Feature                  | n     | %   |
|---------------------------------------------|-------|------------|--------------------------|-------|-----|
| Total white [ $\times 10^3/\mu\text{L}$ ]   | 17500 | 8700-28200 | Leukocytosis $>1\ 000$   | 15/16 | 94  |
| Neutrophil [ $\times 10^3/\mu\text{L}$ ]    | 13677 | 7705-22860 | Neutrophilia $>6500$     | 14/15 | 93  |
| Lymphocyte [ $\times 10^3/\mu\text{L}$ ]    | 2319  | 528-9100   | Lymphopaenia $<1500$     | 5/13  | 38  |
| Haemoglobin [g/dL]                          | 10.7  | 6.8-14.7   | Anaemia $<12.0$          | 11/16 | 69  |
| Platelet [ $\times 10^6/\mu\text{L}$ ]      | 425   | 175-862    | Thrombocytosis $>440$    | 8/16  | 50  |
| Sodium [mmol/L]                             | 133   | 126-142    | Hyponatraemia $<13\ 5$   | 12/15 | 80  |
| Serum osmolality (calc) [mOsm/kg]           | 277   | 193-300    | Hypo-osmolar $<275$      | 2/15  | 13  |
| Albumin [g/L]                               | 34    | 22-38      | Hypoalbuminaemia $<37$   | 14/16 | 88  |
| Globulin [g/L]                              | 40    | 26-50      | Hyperglobulinaemia $>35$ | 14/15 | 93  |
| $\beta_2$ microglobulin [ $\mu\text{g/L}$ ] | 2980  | 1629-7545  | Raised $>1900$           | 5/7   | 71  |
| Bilirubin [ $\mu\text{mol/L}$ ]             | 12    | 5-28       | Raised $>24$             | 2/15  | 13  |
| Alkaline phosphatase [U/L]                  | 207   | 74-836     | Raised $>103$            | 12/16 | 75  |
| Alanine transaminase [U/L]                  | 71    | 9-209      | Raised $>3\ 6$           | 8/15  | 53  |
| Aspartate transaminase [U/L]                | 75    | 19-375     | Raised $>33$             | 9/15  | 60  |
| Lactate dehydrogenase [U/L]                 | 2167  | 447-5205   | Raised $>3\ 80$          | 4/4   | 100 |
| Creatine kinase [U/L]                       | 26    | 19-28      | Normal $<164$            | 12/12 | 100 |
| Aldolase [U/L]                              | 23    | 16.0-35.4  | Raised $>12$             | 10/10 | 100 |
| Uric acid [ $\mu\text{mol/L}$ ]             | 283   | 199-418    | Raised $>446$            | 0/7   | 0   |
| Rheumatoid factor'                          |       |            | Positive                 | 0/15  | 0   |
| Antinuclear factor                          |       |            | Positive $>1:100$        | 2/16  | 13  |
| Erythrocyte sedimentation rate [mm/h]       | 124   | 52-340     | Raised $>15$             | 16/16 | 100 |
| C-reactive protein [mg/L]                   | 132   | 48-249     | Raised $>10$             | 14/14 | 100 |
| Complement 3 [g/L]                          | 1.56  | 1.04-2.24  | Raised $>1.28$           | 7/12  | 58  |
| Complement 4 [g/L]                          | 0.34  | 0.17-0.43  | Raised $>0.72$           | 0/12  | 0   |
| Ferritin [ $\mu\text{g/L}$ ]                | 11163 | 245-130000 | Raised $>179$            | 14/14 | 100 |

not require prednisolone to control disease manifestations, while about half had a slow-acting anti-rheumatic drug (SAARD) added as a steroid-sparing agent. Intravenous pulse cyclophosphamide therapy was given to 2 patients with interstitial lung disease showing ground glass changes on high-resolution computed tomography of the thorax.

#### *Clinical Course and Outcome*

Five patients were lost to follow-up: 3 returned to their home country after diagnosis, while another 2 requested to be discharged to the polyclinics (primary healthcare). The remaining 11 patients had a mean duration of follow-up of 23 months. Of these, 9 relapsed within a year of diagnosis. Most flares involved fever with arthritis/arthralgia or rash in about equal proportions.

Over three-quarters of the patients did not suffer any permanent damage or disability, despite the majority experiencing flares periodically. The only major organ showing irreversible impairment was the lung, with the patients complaining of dyspnoea on moderate exertion, and lung function tests showing persistently diminished  $DL_{CO}$  and a mild restrictive pattern. Liver function tests eventually normalised in all the patients who had hepatic derangement when the disease was active, with no evidence of chronic liver disease. There was no mortality.

#### **Discussion**

Adult-onset Still's disease is a rare and not well-recognised clinical entity, and a study<sup>7</sup> ascertaining its incidence at 0.16 per 100 000 is regarded as grossly under-estimated. It is found in Western series to affect predominantly young adults aged 16 to 35 years, without any gender predilection.<sup>4</sup> Our series, in contrast, has overwhelmingly more females (13:3), more skewed than that noted among the Japanese (2:1).<sup>5</sup> The age of onset of illness is also older in our series.

A proposed pathogenetic model consists of an infective trigger precipitating immune dysregulation in HLA-susceptible individuals, resulting in circulating immune-complexes causing non-necrotizing vasculitis.<sup>6</sup> Antecedent infections reported anecdotally include rubella, parvovirus B19, echovirus, hepatitis C virus, cytomegalovirus, Epstein-Barr virus, yersinia enterocolitica, mycoplasma pneumoniae, leprosy and toxoplasmosis.<sup>4,5,7,8</sup> Despite often exhaustive serological and microbial investigations undertaken in most if not all of our cases to exclude an infective cause, only one case of parvovirus B19 preceded and could possibly have triggered Still's disease. Other disease associations observed varied from rheumatic (Sjogren's syndrome and Takayasu's disease) to neoplastic (myelodysplastic syndrome, immunoblastic non-Hodgkin's lymphoma and haemophagocytic syndrome). One patient in our series

had systemic lupus erythematosus, which has been quiescent for 10 years and did not relapse at onset of Still's disease.

Still's disease is classically described as a triad of:

- 1) spiking and remitting fever often exceeding 39°C,
- 2) evanescent, non-pruritic, salmon-pink, maculopapular rash over trunk and proximal extremities, and
- 3) oligo/polyarthralgia or arthritis of mainly non-axial joints.

All our patients demonstrated the typical febrile spike which is often nocturnal, with accompanying intensification of both the rash and the arthralgia. Eighty per cent of our patients developed rashes during the course of their disease, the majority being the typical salmon-pink enanthem. In addition, up to half of those with rash had pruritus, and the rashes resolved with post-inflammatory hyperpigmentation and fine exfoliation. As such, it may occasionally be mistakenly dismissed as a drug rash.<sup>4</sup> While all our patients experienced arthralgia, only 80% had arthritis. The arthritis was similar to that reported by other authors in that it was generally transient, non-erosive and non-deforming, though some have reported a progressively destructive and disabling form in a minority with chronic disease. Minor manifestations of adult-onset Still's disease include lymphadenopathy, hepatosplenomegaly, serositis, pneumonitis, myalgia and weight loss. Rare manifestations like aseptic meningitis, neuropathy, iritis, interstitial nephritis, sicca syndrome and thrombotic thrombocytopenic purpura have also been reported,<sup>4,5,9,10</sup> but were not seen in our cohort of patients. The unusual complications in our series included interstitial lung disease (2 cases) and overt SIADH (2 cases), the latter only reported once previously in the literature.<sup>11</sup>

Table III summarises the prevalence of various clinical features condensed from Western series,<sup>4,10,12</sup> a Japanese series,<sup>5</sup> and our own, which is generally comparable; except that we have a preponderance of females, patients are older at disease onset, are less symptomatic with regard to sore throat and abdominal pain, and seem to have a lower incidence of serositis. Overall, our features are more similar to those reported by the Japanese, who have reported significant differences from Western data.

Acute phase reactants (platelet count, complements, erythrocyte sedimentation rate, C-reactive protein and ferritin) are elevated,<sup>12</sup> with some investigators claiming that a hyperferritinaemia of over 1000 µg/l may well act as a surrogate diagnostic and activity marker of this disease which is otherwise devoid of pathognomonic serological markers.<sup>5,13-15</sup> In our series, 50% had ferritin in this range, with one measuring 130 000 µg/l. One study suggests that differential glycosylation and sialylation of the isoforms may help to further discriminate adult-

TABLE III: COMPARISON OF CLINICAL FEATURES BETWEEN WESTERN,<sup>4,10,12</sup> JAPANESE<sup>5</sup> AND PRESENT SERIES

| Feature                     | Percentage of study population (%) |          |       |
|-----------------------------|------------------------------------|----------|-------|
|                             | Western                            | Japanese | Local |
| Female                      | 51                                 | 67       | 81    |
| Age of onset 16 to 35 years | 76                                 | 61       | 53    |
| Arthralgia                  | 100                                | 100      | 100   |
| Arthritis                   | 94                                 | 72       | 94    |
| Sore throat                 | 92                                 | 70       | 50    |
| Rash                        | 88                                 | 97       | 81    |
| Myalgia                     | 84                                 | 56       | 50    |
| Asthenia / weight loss      | 76                                 | 56       | 50    |
| Lymphadenopathy             | 63                                 | 69       | 50    |
| Splenomegaly                | 52                                 | 65       | 38    |
| Abdominal pain              | 48                                 |          | 6     |
| Hepatomegaly                | 42                                 | 48       | 38    |
| Pleuritis                   | 31                                 | 12       | 13    |
| Pericarditis                | 30                                 | 10       | 6     |
| Pneumonitis                 | 27                                 |          | 25    |
| Alopecia                    | 24                                 |          |       |

onset Still's disease from other systemic diseases.<sup>13</sup> A mild mixed hepatitic picture with hypoalbuminaemia is common, and cases of fatality from hepatic necrosis have been reported.<sup>4,16</sup> Viral and lupoid hepatitic markers are not usually positive to incriminate these other diseases as likely causes of the hepatitis. It has been suggested that NSAIDs used in treating the fever and arthritis may serve to unmask rather than cause the Still's-associated hepatic dysfunction.<sup>6,16,17</sup>

We observed an elevation of aldolase and lactate dehydrogenase levels during periods of active disease. Commonly considered a muscle enzyme, aldolase is also elevated in other major organ damage such as hepatitis, pancreatitis and haemolysis. Given the normal creatine kinase levels in our cases, we suggest that the raised aldolase may reflect smothering major organ damage, possibly from hepatitis and oxidative haemolysis, rather than myositis. This hypothesis that an increased oxidative stress contributes significantly to the anaemia and hepatitis observed needs to be tested. Other studies comparing these serum enzyme levels in active Still's disease to inactive Still's as well as other similarly intense inflammatory conditions (e.g. reactive arthritis and rheumatoid arthritis) may help to elucidate the value of aldolase and lactate dehydrogenase as disease activity markers.

Interestingly, apart from the two cases of overt SIADH, most had mild hyponatraemia and low-normal calculated serum osmolality, possibly reflecting an occult SIADH in intense or prolonged inflammation. Again, further studies can be undertaken to determine if this phenomenon is present in other similar inflammatory conditions like infections and rheumatoid arthritis.

NSAIDs constitute the first-line treatment for the arthritis and fever, and about a quarter of patients do respond.<sup>4,9,10,17,18</sup> Concerns of aggravating or precipitating hepatitis and intravascular coagulation<sup>4,9</sup> oblige that its use in patients with hepatic abnormalities be closely monitored with frequent liver function tests and clotting profiles.

Most clinicians would add or replace with prednisolone for patients who have hepatic derangement or who fail to respond adequately to NSAIDs,<sup>4,9,10,17</sup> the latter situation resulting in almost 90% of our patients as well as in another series requiring corticosteroids.<sup>19</sup> However, absolute indications for steroid use are a worsening transaminitis while on NSAIDs, and in life-threatening situations [e.g. myocarditis and disseminated intravascular coagulation (DIC)].<sup>12</sup> As in other series, our patients (about half) eventually received slow-acting anti-rheumatic drugs and immunosuppressive agents for progressive arthritis, interstitial lung involvement and as a steroid-sparing agent in chronic relapsing disease.<sup>4,20,21</sup>

Given the rarity of this disease, prospective data on prognosis are scarce but suggest a favourable outcome.<sup>4,17,22</sup> None of our patients had deforming arthritis so far. The 2 patients with lung involvement had mild persistent impairment of gaseous diffusion capacity. However, over 80% of our patients remaining on our follow-up experienced flares of their disease mainly fever and arthritis. Polyarthritis and the development of Still's rash at onset,<sup>4,17</sup> the involvement of girdle joints,<sup>4</sup> the presence of autoantibodies,<sup>4</sup> and a poor response to NSAID alone as therapy<sup>4</sup> were found to prognosticate for chronic disease and a worse outcome.

## Conclusion

Adult-onset Still's disease is a rare and under-recognised rheumatic disease. Although it remains a diagnosis of exclusion, it possesses characteristic features which would allow for earlier diagnosis and effective treatment, and thus save the patient the trauma of extensive costly investigations and protracted unameliorated disease. Apart from a female preponderance, an older age at onset and fewer patients with abdominal pain, myalgia, sore throat and serositis in our series, we found the clinical manifestations and course to be fairly uniform worldwide, and outcome for the majority is good, compared to the other chronic arthritides.

## REFERENCES

1. Bywaters E G L. Still's disease in the adult. *Ann Rheum Dis* 1971; 30:121-32.
2. Ansell B. In: Schumacher Jr H R, editor. *Primer on the Rheumatic Diseases*. 10th ed. USA: Arthritis Foundation, 1993:182-3.
3. Magadur-Jolly G, Billaud E, Barrier J H, Pennec Y L, Masson C, Renou I, et al. Epidemiology of adult Still's disease: estimate of the incidence by a

- retrospective study in west France. *Ann Rheum Dis* 1995; 54:587-90.
4. Pouchot J, Sampalis JS, Beaudet F, Carette S, Decary F, Salusinsky-Sternbach M, et al. Adult Still's disease: manifestations, disease course and outcome in 62 patients. *Medicine (Baltimore)* 1991; 70:118-36.
  5. Ohta A, Yamaguchi M, Tsunematsu T, Kasukawa R, Mizushima H, Kashiwagi H, et al. Adult onset Still's disease: a multicentre survey of Japanese patients. *J Rheumatol* 1990; 17:1058-63.
  6. Elkon KB, Hughes GR V, Bywaters E G L, Ryan P F, Inman R D, Bowley N B, et al. Adult-onset Still's disease: Twenty-year follow-up and further studies of patients with active disease. *Arthritis Rheum* 1982; 25:647-54.
  7. Wouters J M G W, van der Veen J, van de Putte L B A, de Rooij D J R A M. Adult onset Still's disease and viral infections. *Ann Rheum Dis* 1988; 47:764-7.
  8. Pouchot J, Ouakil H, Debin M L, Vinceneux P. Adult Still's disease associated with acute human parvovirus B19 infection [letter]. *Lancet* 1993; 341:1280-1.
  9. Reginato A J, Schumacher H R, Baker Jr D G, O'Connor C R, Ferreiros J. Adult onset Still's disease: experience in 23 patients and literature review with emphasis on organ failure. *Semin Arthritis Rheum* 1987; 17:39-57.
  10. Ohta A, Yamaguchi M, Kaneoka H, Nagayoshi T, Hiida M. Adult Still's disease: review of 228 cases from the literature. *J Rheumatol* 1987; 14:1139-46.
  11. Esdaile J M, Tannenbaum H, Hawkins D. Adult Still's disease. *Am J Med* 1980; 68:825-30.
  12. Honjoh H, Kobayashi S, Okada H, Ikeda T. SIADH in a patient with pleurisy related to adult onset Still's disease. *Clin Nephrol* 1995; 44:400-1.
  13. Esdaile J M. Adult Still's disease. In: Klippel J H, Dieppe P A, editors. *Rheumatology*. 2nd ed. USA: Mosby International, 1997; 5:22:1-8.
  14. Van Reeth C, Le Moel G, Lasne Y, Revenent M C, Agneray J, Kahn M F, et al. Serum ferritin and isoferitins are tools for diagnosis of active adult Still's disease. *J Rheumatol* 1994; 21:890-5.
  15. Blasa Criado A, Niguel-Mendieta E. Serum ferritin can be useful in adult onset Still's disease. *J Rheumatol* 1989; 16:412-3.
  16. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, et al. Preliminary criteria for classification of adult Still's disease. *J Rheumatol* 1992; 19:424-30.
  17. Esdaile J M, Tannenbaum H, Lough J, Hawkins D. Hepatic abnormalities in adult onset Still's disease. *J Rheumatol* 1979; 6:673-9.
  18. Cush J J, Medsger Jr T A, Christy W C, Herbert D C, Cooperstein L A. Adult-onset Still's disease: clinical course and outcome. *Arthritis Rheum* 1987; 30:186-94.
  19. Larson E B. Adult Still's disease. Evolution of a clinical syndrome and diagnosis, treatment, and follow-up of 17 patients. *Medicine (Baltimore)* 1984; 63:82-91.
  20. Masson C, Le Loet X, Liote F, Renou P, Dubost J J, Boissier M C, et al. Adult Still's disease: management, outcome and prognostic factors. *Revue Du Rhumatisme (English edition)* 1995; 62:758-65.
  21. Aydintug A O, D'Cruz D, Cervera R, Khamashta M A, Hughes G R V. Low dose methotrexate treatment in adult Still's disease. *J Rheumatol* 1992; 19:431-5.
  22. Sampalis J S, Esdaile J M, Medsger Jr T A, Partridge A J, Yeadon C, Senlecal J L, et al. A controlled study of the long-term prognosis of adult Still's disease. *Am J Med* 1995; 98:384-8.