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Clinical features of elderly-onset Adult-onset Still’s disease

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ABSTRACT

Objectives: To clarify the characteristics of patients with elderly-onset Adult-onset Still’s disease (AOSD).

Methods: Patients were classified into elderly-onset (≥ 60 years: 47 patients) and younger-onset (< 60 years: 95 patients) groups according to their age at diagnosis of AOSD. Clinical features, treatments, and prognosis were compared between the elderly-onset and younger-onset groups.

Results: In the elderly-onset group, compared with the younger-onset group, typical skin rash and more frequent (21.3% vs 58.9%, respectively; \(p < .0001\)) were less frequent (21.3% vs 58.9%, respectively; \(p < .0001\)), whereas pleuritis (27.7% vs 7.4%, respectively; \(p = .0011\)) was disseminated intravascular coagulation (19.1% vs 2.1%, respectively; \(p = .0004\)) were more frequent, and serum ferritin levels were higher (median 12,700 ng/ml vs 2526 ng/ml, respectively; \(p < .0001\)). Overall survival and AOSD-related survival were reduced (\(p = .0006\) and \(p = .0023\), respectively) and drug-free remission was less frequent (\(p = .0035\)) in the elderly-onset group compared with the younger-onset group.

Conclusions: Our results demonstrated that elderly-onset AOSD patients had several characteristics that differed from younger-onset AOSD patients, including less typical skin lesions, more AOSD-related complications, higher ferritin levels, and poorer prognoses.

Introduction

Adult-onset Still’s disease (AOSD) is a systemic inflammatory disease with spiking fever, arthritis, and evanescent rash as its three main symptoms. Typical laboratory data for AOSD patients include leukocytosis and neutrophilia, elevated transaminase and C-reactive protein (CRP) levels, no autoantibodies, and hyperferritinemia [1,2]. The etiology and pathogenesis of the inflammatory response in AOSD are still unclear, but it is thought that the excessive production of cytokines, including interleukin (IL)-1, IL-6, IL-18, tumor necrosis factor-\(\alpha\), and interferon-\(\gamma\), produced by macrophages and T cells, plays important roles [3]. AOSD generally develops in young adults; the mean age at onset in the 30s [4–6]. However, the distribution of age at diagnosis has shifted recently towards older age groups in Japan [7,8]. Case reports of elderly-onset patients with AOSD have been reported, and a review of them has suggested several features associated with these patients, such as a higher frequency of complications and poor survival [9–15]. However, there are an insufficient number of cases to explore the clinical features of elderly-onset patients with AOSD, and therefore our knowledge is still limited. In this study, we analyzed the clinical features and outcomes of patients with elderly-onset AOSD and compared them with those of patients with younger-onset AOSD in a retrospective multi-institutional study.

Patients and methods

We retrospectively reviewed the medical records of AOSD patients who were hospitalized and diagnosed at four university hospitals and affiliated hospitals between January 2006 and September 2016. Diagnosis of AOSD was made according to Yamaguchi’s classification criteria [16]. We defined the elderly-onset group as patients who were diagnosed with AOSD over the age of 60 years according to the age distribution of study patients (Figure 1). This study was approved by the Saga University Hospital Ethics Committee (#2016-11-15) and was registered with UMIN (trial registration number: UMIN000024945). Informed consent was obtained with an opt-out.
Survival curves were calculated using the Kaplan–Meier test or Student’s t-test. A contingency table test (chi-square) was performed using a contingency table test (chi-square data were expressed as percentages. Statistical evaluation was based on a normal distribution for normally distributed data. Categorical data were expressed as percentages. Statistical evaluation was based on either criteria for autoimmune-associated hemophagocytic syndrome described by Kumakura et al. [17], the HLH-2004 guidelines [18], or classification criteria for MAS in patients with AOSD that we proposed recently [19]. The diagnosis of disseminated intravascular coagulation (DIC) was made based on the diagnostic criteria of the Japanese Society on Thrombosis and Hemostasis [20]. The severity was evaluated using the systemic score [21] and the severity index (Japanese Ministry of Health, Labour and Welfare). The latter was calculated as the sum of the following scores, serositis (1), DIC (2), MAS (2), neutrophil ratio ≥85% (1), serum ferritin ≥3000 ng/ml (1), prominent lymphadenopathy (1), and refractoriness to corticosteroid therapy (≥0.4 mg/kg of prednisolone) (1). We defined drug-free remission as remission of AOSD in the absence of any immunosuppressive drugs, including corticosteroids, that lasted at least six months. Time to drug-free remission was the duration between the diagnosis and the termination of the immunosuppressive treatment against AOSD.

In addition, we also examined clinical differences between female and male patients, because female patients were dominant in the elderly-onset group.

**Statistical analysis**

Results from continuous variables were presented as the median with 25th and 75th percentiles or the mean and standard deviation for normally distributed data. Categorical data were expressed as percentages. Statistical evaluation was performed using a contingency table test (chi-square test) to identify significant differences. The Mann–Whitney U test or Student t-test were used for quantitative variables. Survival curves were calculated using the Kaplan–Meier method and the log-rank test was used to identify differences. All statistical analyses were performed using Prism version 7 software (GraphPad, San Diego, CA, USA).

**Results**

The study population consisted of 103 female patients and 39 male patients, and age at diagnosis was 17–88 years old. The distribution of age showed a bimodal pattern (Figure 1(a)); there was one peak age in the 30s and another in the 60s. The distribution was different between males and females, i.e. elderly-onset patients were predominantly female (Figure 1(b,c)). From these results, we defined the elderly-onset group as patients diagnosed with AOSD after the age of 60 (47 patients) and the younger-onset group as those diagnosed at 60 years or younger (56 patients).

**Clinical features and severity in the elderly-onset and younger-onset groups**

Clinical features are summarized in Table 1. The elderly-onset group consisted of 39 female and eight male patients, and the younger-onset group consisted of 64 female and 31 male patients. Although not significant, female patients were more predominant in the elderly-onset group (83.0% vs 72.6%, respectively; *p* = 0.566). The mean age at diagnosis of AOSD was 71.2 ± 7.3 years and 37.7 ± 12.1 years (*p* < .0001) in the elderly-onset and younger-onset groups, respectively. The time from onset to diagnosis varied in patients, but there was no difference between the two groups (median 33.0 days vs 28.0 days, respectively, *p* = .6633). Elderly-onset patients showed a lower frequency of typical skin rashes (21.3% vs 58.9%, respectively; *p* < .0001) and sore throats (55.3% vs 72.6%, respectively; *p* = .0391), whereas they developed more complications including pleuritis (27.7% vs 7.4%, respectively; *p* = .0011) and DIC (19.1% vs 2.1%, respectively; *p* = .0004) compared with younger-onset patients. The frequency of MAS was not statistically different between the two groups (17.0% vs 10.5%, respectively; *p* = .2737). Although the systemic score was similar in the two groups (5.96 ± 1.63 vs 5.68 ± 1.69, respectively; *p* = .9430), the severity index was higher in the elderly-onset group than in the younger-onset group (3.06 ± 1.90 vs 2.05 ± 1.48, respectively; *p* = .0035) because of the large number of patients in elderly-onset group who developed serositis and DIC.

**Figure 1.** Age distribution of patients with Adult-onset Still’s disease. (a) Total patients. (b) Female patients. (c) Male patients.
Table 2 shows the comparison of laboratory data between onset groups. Laboratory data of the elderly-onset and younger-onset groups. In the elderly-onset group, hemoglobin levels (median 11.0 g/dl vs 7.0 g/dl, respectively); aspartate aminotransferase (AST) (73.5 U/L vs 45.0 U/L, respectively); alanine aminotransferase (ALT) (6.3 U/L vs 1.1 U/L, respectively); total protein (6.50 g/dl vs 4.49 g/dl, respectively; p = .0001). However, serum ferritin did not correlate with complications. As shown in Figure 2, compared with non-MAS patients, patients with MAS showed higher ferritin levels in the elderly-onset group (median 26,286 ng/ml vs 8375 ng/ml, respectively, p = .0001). Because the high serum ferritin levels in the elderly-onset group were remarkable, we analyzed the association between serum ferritin and clinical features or inflammatory markers. As shown in Figure 2, compared with non-MAS patients, patients with MAS showed higher ferritin levels in the elderly-onset group (median 26,286 ng/ml vs 8375 ng/ml, respectively, p = .0001). However, serum ferritin levels were still higher in the elderly-onset group than in the younger-onset group (median 7943 ng/ml vs 2492 ng/ml, respectively, p < .0001, Figure 2). On the other hand, serum ferritin did not correlate with CRP or Erythrocyte sedimentation rate (ESR) (Supplementary Figure 1), which may explain why CRP and ESR levels were similar between the two groups.

Treatments in the elderly-onset and younger-onset groups

Treatments during the first remission induction were compared between the elderly-onset and younger-onset groups (Table 3). Cyclosporine was more frequently used in the elderly-onset group compared with the younger-onset group (61.7% vs 41.1%, respectively; p = .0205). Maximal doses of prednisolone and the frequency of use of methylprednisolone pulse therapy, methotrexate, and biological agents were not different between the two groups. Plasma exchange was performed in four patients in the elderly-onset group and one patient in the younger-onset group (8.5% vs 1.1%, respectively; p = .0233). All patients had MAS and/or DIC complications.

Prognosis and drug-free remission in the elderly-onset and younger-onset groups

Survival was significantly reduced in the elderly-onset group compared with the younger-onset group (p = .0006, Figure 3(a)). Seven elderly-onset patients (14.9%) and one younger-onset patient (1.1%) died. Causes of death in the elderly-onset group were as follows: pneumonia (two patients), sepsis, sepsis with pneumocystis pneumonia and aspergillosis, cytomegalovirus infection and AOSD, subarachnoid hemorrhage, and breast cancer. The cause of death in the younger-onset patient was subarachnoid hemorrhage. AOSD-related death was observed only in the elderly-onset group (five patients), and the cause of death was infection. Their disease was refractory to corticosteroids and four
patients had systemic complications (pleuritis three, MAS one, and DIC one). Cyclosporine was given to all patients, and biological agents (tocilizumab and etanercept) were administered to one patient. Three patients died in the early period (4.1 years and 5.9 years). The AOSD-related mortality rate was 10.6% (5/47) in the elderly-onset group, which was also significantly reduced using the log-rank test (p < .0001, Figure 3(b)). We analyzed the time course of drug-free remission. As shown in Figure 3(c), less elderly-onset patients achieved drug-free remission compared with younger-onset patients (p = .0035, Figure 3(c)); the five-year drug-free remission rate was 14.7% in the elderly-onset group and 45.6% in the younger-onset group. Among 46 patients that achieved drug-free remission, one patient in the elderly-onset group and three patients in the younger-onset group had recurrences. Periods from the date of withdrawal of therapy to recurrence were 3.8 years in the elderly-onset group, and 7 months, 3 years, and 5 years in the younger-onset group.

**Comparison of clinical features, therapy, and prognosis between female and male patients**

Because most elderly-onset patients were female, we considered that the characteristics of the elderly-onset group might be influenced by a sex bias. Therefore, we compared clinical features, therapy, and prognosis between female and male patients. The mean age at diagnosis of female patients at diagnosis was higher than that of male patients (51.3 ± 19.2 years vs 42.3 ± 17.8 years, respectively) (Supplementary Table 1). However, the frequency of clinical findings and complications as well as severity was not different between female and male patients (Supplementary Table 1). Serum ferritin also showed similar levels between groups (4592 ng/ml vs 2945 ng/ml, respectively; p = .5629) (Supplementary Table 2). Methylprednisolone pulse therapy was more frequently used (33.0% vs 15.4%, respectively; p = .0390) and methotrexate less frequently used (15.5% vs 33.3%, respectively; p = .0338) in female patients compared with male patients (Supplementary Table 3). Survival was not significantly different, but drug-free remission was infrequent in female patients (p = .0328) (Supplementary Figure 2). These results indicated that notable characteristics found in the elderly-onset group, including frequency of typical skin rashes, pleuritis, DIC, serum ferritin levels, and prognosis, were not different between male and female patients.

**Discussion**

In this study, we confirmed that age at disease onset influenced the clinical manifestations, complications, and outcomes of patients with AOSD. Elderly-onset AOSD was characterized by the following: rare typical skin rashes, elevated frequency of pleuritis and DIC, and very high levels

### Table 2. Laboratory and immunologic findings.

<table>
<thead>
<tr>
<th>n</th>
<th>Elderly-onset Group (n = 47)</th>
<th>Younger-onset Group (n = 95)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells (×10^9/mm^3)</td>
<td>1400 (10200, 17600)</td>
<td>11950 (8800, 15500)</td>
<td>.0878</td>
</tr>
<tr>
<td>Neutrophils (×10^9/mm^3)</td>
<td>12844 (8512, 15651)</td>
<td>10358 (6906, 13761)</td>
<td>.0102</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.0 (10.0, 11.9)</td>
<td>11.4 (10.3, 12.5)</td>
<td>.0328</td>
</tr>
<tr>
<td>Platelet (×10^3/mm^3)</td>
<td>25.3 (20.2, 37.3)</td>
<td>28.6 (20.4, 34.7)</td>
<td>.4927</td>
</tr>
<tr>
<td>C-reactive protein (mg/dl)</td>
<td>10.57 (5.57, 17.29)</td>
<td>10.02 (6.23, 16.46)</td>
<td>.8164</td>
</tr>
</tbody>
</table>

The median and 25th and 75th percentiles in parenthesis are shown.

*Number of patients and (%).

ESR, Erythrocyte sedimentation rate; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; ALP, Alkaline phosphatase; ANA, Anti-nuclear antibody.

*p < .05, **p < .01, ***p < .001, ****p < .0001.
of serum ferritin. In addition, their survival was worse and drug-free remission was less frequent than those of younger-onset patients.

It was reported that AOSD develops mainly in young adults, and the mean age at onset is in the 30s [4–6]. However, recent investigations have revealed that the age distribution at diagnosis of AOSD has shifted toward an older age in Japan. This may be because of aging of the general population but our analyses showed a bimodal distribution in the elderly-onset group. A previous study also showed a similar distribution [8]. It is difficult to explain this pattern based on endogenous female hormone levels, and this should be further confirmed in a larger cohort.

Although case reports of elderly-onset patients with AOSD are increasing, the present study is the first medium-scale investigation carried out with a detailed analysis of many parameters, including survival and drug-free remission. A review of previous case reports described several potential characteristics of elderly-onset patients with AOSD, such as a high incidence of DIC and poor survival [15], some of which were confirmed in the present study. A low incidence of typical skin rashes but an increased frequency of atypical skin lesions that occurred in elderly-onset AOSD patients is noteworthy. Atypical skin lesions include persistent papules, plaques or erythema, urticarial rash, and dermatomyositis-like plaques [22]. In a review of AOSD with atypical cutaneous manifestations, the authors showed that most of these patients required strong immunosuppressive therapy, and that the development of atypical manifestations seemed to be associated with a potentially worse prognosis because of infectious complications related to therapy [22]. These features were consistent with those of elderly-onset patients, as shown in this study, although an association between atypical skin lesions and age has not been reported. This should be considered when diagnosing late-onset AOSD.

Pleuritis, which was reported to be associated with AOSD at a frequency of 4%–50% [5,7], occurred more often in the elderly-onset group. To date, similar findings have not been reported for AOSD, but serositis is known as one of the frequent clinical features in late-onset systemic lupus erythematosus, [23]. DIC, a life-threatening complication caused by an activation of the coagulation system, is a rare complication in AOSD. A literature review suggested that a higher incidence of DIC was one of the characteristics of elderly-onset AOSD [15], which supports our results. In addition, although the frequency of MAS was not

### Table 3. Treatment regimens.

<table>
<thead>
<tr>
<th></th>
<th>Elderly-onset Group (n = 47)</th>
<th>Younger-onset Group (n = 95)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone (PSL)</td>
<td>47 (100)</td>
<td>95 (100)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Maximal dose (mg/day)*</td>
<td>44.0 ± 17.8</td>
<td>47.5 ± 18.7</td>
<td>.2982</td>
</tr>
<tr>
<td>Methylprednisolone pulse therapy</td>
<td>19 (39.6)</td>
<td>22 (23.2)</td>
<td>.0591</td>
</tr>
<tr>
<td>Methotrexate (MTX)</td>
<td>6 (12.8)</td>
<td>23 (24.2)</td>
<td>.1114</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>29 (61.7)</td>
<td>39 (41.1)</td>
<td>.0205*</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>3 (6.4)</td>
<td>4 (4.2)</td>
<td>.5736</td>
</tr>
<tr>
<td>Other immunosuppressants*</td>
<td>3 (6.4)</td>
<td>3 (3.2)</td>
<td>.3384</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
<td>1 (2.2)</td>
<td>1 (1.1)</td>
<td>.6090</td>
</tr>
<tr>
<td>Biological agents</td>
<td>5 (12.5)</td>
<td>15 (15.8)</td>
<td>.4063</td>
</tr>
<tr>
<td>Anti-TNF drugs</td>
<td>4 (8.5)</td>
<td>3 (3.2)</td>
<td>.1656</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>2 (4.3)</td>
<td>13 (13.7)</td>
<td>.0854</td>
</tr>
<tr>
<td>Plasma exchange</td>
<td>4 (8.5)</td>
<td>1 (1.1)</td>
<td>.233*</td>
</tr>
<tr>
<td>PSL only</td>
<td>14 (29.8)</td>
<td>41 (43.2)</td>
<td>.1238</td>
</tr>
<tr>
<td>PSL + MTX</td>
<td>3 (6.4)</td>
<td>13 (13.7)</td>
<td>.1954</td>
</tr>
<tr>
<td>PSL + Calcineurin inhibitors</td>
<td>27 (57.4)</td>
<td>31 (32.6)</td>
<td>.0046**</td>
</tr>
<tr>
<td>PSL + MTX + Calcineurin inhibitors</td>
<td>3 (6.4)</td>
<td>10 (10.5)</td>
<td>.4205</td>
</tr>
</tbody>
</table>

The number of patients and percentages (%) are shown.
*Mean and SD.
Azathioprine (n = 2) and mizoribine (n = 1) in the elderly-onset group; intravenous cyclophosphamide in the younger-onset group (n = 3).
*p < .05, **p < .01.

### Figure 3. Survival and drug-free remission of patients with Adult-onset Still’s disease. (a) Overall survival is shown. Kaplan–Meier analysis shows a reduced survival in the elderly-onset group compared with the younger-onset group (p = .0008). (b) AOSD-related survival. Kaplan–Meier analysis shows a reduced survival in the elderly-onset group compared with the younger-onset group (p = .0023). (c) Time course of drug-free remission. Kaplan–Meier analysis shows a reduced drug-free remission rate in the elderly-onset group compared with the younger-onset group (p = .0035).
significantly different between groups, serum ferritin levels were remarkably higher in the elderly-onset group. Of note, CRP and ESR levels were not different between the two groups and these did not correlate with ferritin levels. These data indicated that elevated ferritin levels do not just reflect accelerated inflammation. It was reported that hyperferritinemia is a hallmark of non-chronic arthritis type AOSD, in which MAS, DIC, and serositis are complications [24]. In this study, patients associated with MAS and DIC had higher levels of ferritin and were more frequent in the elderly-onset group (27.7%) than in the younger-onset group (11.6%). Furthermore, serum ferritin levels in patients without MAS or DIC were still higher in the elderly-onset group compared with the younger-onset group. These results suggest that elderly-onset patients are more vulnerable to macrophage activation that induces MAS and DIC.

We did not find many differences in treatment between the elderly-onset and younger-onset groups, except for cyclosporine that was more frequently used in the elderly-onset group. Calcineurin inhibitors were used in 64% of elderly-onset patients and 46% of younger-onset patients. These drugs were apparently used mainly to control associated complications; 19 patients out of 30 exhibited MAS, DIC, or serositis. Cyclosporine is a first-line immunosuppressive drug used for MAS [25,26]. There were no differences in the use of biological agents between the two groups. These drugs are highly effective in the treatment of AOSD and the frequency of their use is increasing [6]. Tocilizumab, a preferred biological agent in Japan [27,28], is somewhat less frequently administered to the elderly-onset group, presumably because of concerns about its adverse effects, especially infection.

Overall survival and AOSD-related survival of elderly-onset patients were worse than those of younger-onset patients. The cause of death was infection, and most of these patients had complications that were treated with immunosuppressive drugs. From these results, strong immunosuppressive therapy should be used with extreme caution in elderly-onset patients. Previous studies identified poor prognostic factors of AOSD, including MAS, AOSD-related complications, systemic score, and a lower initial corticosteroid dose [29–31]. However, age at diagnosis has not been reported. This may be due to different patient populations; the mean age at diagnosis ranged from 33 to 45 years in previous reports [29–31] but was 49 years in this study. Because few elderly-onset patients were included in previous studies, they might not have extracted age as a significant factor. Our results regarding survival in elderly-onset patients may be associated with frequent systemic complications in addition to the consequences of aging. Furthermore, drug-free remission was less achievable in the elderly-onset group, which suggests refractory disease in this population. This is a novel finding because the rate of drug-free remission in AOSD has not been reported previously. We are performing another study to analyze critical factors implicated in drug-free remission in AOSD. In addition, a comparison between female and male patients showed very few similar results compared with those between the elderly-onset and younger-onset groups. The frequency of typical skin rashes, pleuritis and DIC, serum ferritin levels, and prognosis was not different between these groups. These results indicate that the aforementioned characteristics in the elderly-onset group are not related to sex bias.

There were several potential biases in the present study. Data were not extracted from a compulsory disease registry but from self-reported information that may be prone to bias. Differential diagnosis, especially in elderly-onset patients, might be difficult. Although we carefully excluded patients with malignant disease, it is possible that, because of the short observation period, we may have included patients whose diagnosis was later changed in other facilities. In addition, although drug-free remission was an important parameter in this analysis, the decision to reduce or terminate therapeutic drugs depended on the attending physician. The age of patients might affect these treatment policies, indicating they might be prone to bias. Furthermore, it is well known that AOSD patients frequently relapse, even after the cessation of corticosteroid treatment. Indeed, some patients were reported to have disease recurrence in this study. Therefore, longer observation may be necessary to analyze drug-free remission.

Conclusion

In conclusion, AOSD can develop in patients over the age of 60 years, especially females. The clinical features of elderly-onset AOSD were characterized by less frequent typical skin lesions, more frequent complications with pleuritis and DIC, and higher ferritin levels. The reduced survival and drug-free remission rate might reflect the consequences of aging, vulnerability to immunosuppressive therapy, and severe disease. Thus, we should pay more attention to the diagnosis and management of elderly-onset patients with AOSD. A large-scale study will be necessary to confirm our results.

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Conflict of interest

M. Iwamoto received royalties from Chugai and speaker’s fees from Sanofi and Lilly. Y. Tada received a speaker’s fee from Chugai.

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