Comparison of complications during 1-year follow-up between remitting seronegative symmetrical synovitis with pitting edema syndrome and elderly-onset rheumatoid arthritis

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1. Introduction

Remitting seronegative symmetrical synovitis with pitting edema syndrome (RS3PE), a rheumatic disease affecting the elderly, responds well to corticosteroids; however, our RS3PE patients’ corticosteroid therapy is longer than expected. Elderly-onset rheumatoid arthritis (EORA) patients are reported to be at a significantly increased risk for steroid-related side effects including cardiovascular diseases (CVDs). To clarify the complications during a 1-year follow-up in corticosteroid-treated RS3PE patients compared to EORA patients. We retrospectively analyzed the records of 47 RS3PE patients (28 men, 19 women; age 78.4 ± 7.5 years) and 46 EORA patients (10 men, 36 women; 77.0 ± 6.8 yrs) to compare the complications over a 1-year follow-up. The RS3PE and EORA groups’ average initial PSL doses were 16.5 ± 7.2 mg/day and 7.3 ± 4.6 mg/day, respectively. During the 1-year follow-up after treatment, there was no significant increase in CVDs in both groups. However, infections occurred in nine RS3PE patients, which is a significantly higher incidence compared to the EORA patients with infections (n = 3). The initial PSL dose was the independent variable associated with the incidence of infection. Infections were significantly increased during elderly RS3PE patients’ steroid therapy. The initial corticosteroid dose was an infection-risk factor.

KEY MESSAGES

- Infections are increased during steroid therapy in elderly patients with RS3PE syndrome.
- The initial dose of corticosteroids was one of the risk factors for infections.
We conducted the present study to compare the incidence of complications during a 1-year follow-up in RS3PE syndrome patients with the corresponding incidence in elderly-onset RA patients, and we investigated whether the patients’ corticosteroid therapy contributed to the complications.

2. Patients and methods

2.1. Patients

We performed a retrospective multicenter study to investigate the incidence of complications during a 1-year follow-up of elderly patients with RS3PE syndrome and elderly patients with RA. Seventy patients who were clinically diagnosed with RS3PE syndrome from 2003 to 2020 were registered in the study (Figure 1). Five patients were excluded as their diagnoses were changed to RA. Four patients were excluded as they did not fulfill the study criteria: (1) bilateral pitting edema of the hands or feet, or both, (2) sudden onset of polyarthritis, (3) age >50 years, and (4) seronegativity for rheumatoid factor (RF). Ten patients were excluded due to a lack of follow-up, and four patients were excluded due to missing data.

We analyzed 47 patients with RS3PE syndrome. As a control, we also included 46 patients with elderly-onset RA (EORA); all RA patients fulfilled the 2010 ACR/EULAR classification criteria for RA and developed RA after the age of 65 years.

The enrolled patients were distinguished from those with polymyalgia rheumatica, or other rheumatic conditions except EORA, including peripheral spondyloarthritis, psoriatic arthritis, puffy finger due to systemic sclerosis or mixed connective tissue diseases (MCTD) for male predominance, predominantly peripheral joint involvement, existence of pitting edema, ultrasonographical findings, absence of skin lesion, Raynaud phenomenon and disease-specific antibodies, and good response to a corticosteroid. Ultrasonography of the extremities showed tenosynovitis as a major cause of subcutaneous edema [5]. The patients were examined by chest X-ray, T-SPOT\textsuperscript{TM} tuberculosis test, and measurements of β-D-glucan, hepatitis B virus antigen, and hepatitis C virus antibody before their treatment. All of the patients gave their informed consent to be subjected to the protocol. The study was approved by the Institutional Review Board of our University and related institutions.

2.2. Main outcome variable

We obtained the clinical characteristics of RS3PE syndrome and EORA from the patients’ medical records. The baseline variables included gender, age at evaluation and age at disease onset, disease duration, tender joint count, swollen joint count, pitting edema, and laboratory data including the white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP) concentration, serum RF concentration, and serum anti-cyclic citrullinated peptide antibody (ACPA) concentration. The initial prednisolone (PSL) dose, the cumulative PSL dose, the methotrexate (MTX) dose, the use of one or more other disease-modifying anti-rheumatic drugs (DMARDs), the prophylaxes for infection, and complications including HT, DM, dyslipidemia, ischemic heart disease (IHD), cerebrovascular disease, infection, and malignancy during the treatment were also examined.

2.3. Study factors

The diagnosis of HT was based on systolic blood pressure >140mmHg, diastolic blood pressure >90mmHg, or the use of antihypertensive medication. The diagnosis of DM was based on the American Diabetes Association diagnostic criteria of

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Figure 1. Flow chart of the RS3PE syndrome patients.
DM, or treatment with hypoglycemic agents [6]. The diagnosis of dyslipidemia was based on low-density lipoprotein (LDL) cholesterol ≥140 mg/dL, high-density lipoprotein (HDL) cholesterol ≤40 mg/dL, triglyceride ≥150 mg/dL, or treatment with lipid-lowering drugs. The prevalence of IHD was defined as a physician’s diagnosis, use of an anti-anginal drug, or hospitalization for IHD. Cerebrovascular diseases were categorized as positive if any of the following diseases were present: cerebral infarction, cerebral hemorrhage, or subarachnoid hemorrhage. The incidence of cerebrovascular diseases was defined as a physician’s diagnosis, magnetic resonance imaging findings, or hospitalization for cerebrovascular disease.

The incidence of infections was defined as a physician’s diagnosis of an infection, treatment for an infection, or hospitalization for an infection. The infections included bacterial infections, viral infections, and fungal infections. The incidence of malignancies was defined as a physician’s diagnosis of the malignancy or surgery for a malignancy. The malignancies were detected by chest and abdominal CT scan, gastrointestinal endoscopy, colonoscopy, or other modalities.

The doses of PSL were determined for each patient by a rheumatologist with >10 years’ experience in the treatment of rheumatic diseases. The doses were determined by referring to not only articular symptoms but also the patient’s serum CRP concentration, ultrasonographic findings, and coexistence of DM.

2.4. Procedures

All patients visited our hospitals between October 2003 and June 2020, and their clinical data were obtained. They were also screened for complications. After 1 year of treatment, the patients’ clinical data and complications were obtained again. We compared the frequencies of the complications during the 1-year follow-up.

We conducted a univariate analysis and a multivariate analysis to identify factors contributing to the patients’ complications. Because we observed that the rate of infections increased significantly during the patients’ 1 year of treatment, we also investigated the risk factors for infections during the 1-year treatment. The variables included in the analysis were sex, age, disease duration, tender joint count, swollen joint count, pitting edema, laboratory data, the PSL dose, the MTX dose, other DMARD use, and prophylaxes for infections.

2.5. Statistical analyses

The incidence of each complication is expressed in terms of the number of patients presenting with the complication (%). The statistical analysis was performed using the χ²-test. The factors contributing to infection with a probability (p)-value <.05 in the univariate analysis were included in a multivariate regression analysis; their results are expressed as the odds ratio (OR) and 95% confidence interval (95%CI). We also included age in multivariate analysis which is important clinical factor contributing to infection. A p-value <.05 was considered significant. All statistical analyses were performed on a personal computer using JMP Pro 16 software (SAS Institute, Cary, NC, USA).

3. Results

3.1. The clinical characteristics of the patients with RS3PE syndrome

The data for 47 patients with RS3PE syndrome out of the original pool of 70 patients were available and analyzed. These patients included 28 men (59.6%) and 19 women (40.4%) with an average age of 78.4 ± 7.5 years. The EORA group included 10 men (21.7%) and 36 women (78.3%) with an average age of 77.0 ± 6.8 years (Table 1). The RS3PE and EORA groups’ average disease durations were 2.0 ± 2.2 and 11.1 ± 14.1 months, respectively.

The RS3PE group’s average ESR and CRP levels before treatment were significantly higher than those in the EORA group at 75.6 ± 35.7 mm/h (p = .0325) and 7.6 ± 5.2 mg/dL (p < .0001), respectively. RF and ACPA were negative in all of the RS3PE patients.

The average initial PSL dose in the RS3PE group was 16.5 ± 7.2 mg/day, which was significantly higher than that in the EORA group (7.3 ± 4.6 mg/day; p < .00001). The average cumulative PSL dose in the RS3PE syndrome group was 3201.6 ± 1059.2 mg, which was also significantly higher than that in the EORA group (998.4 ± 1274.1 mg; p < .00001). All 47 of the RS3PE patients responded dramatically to PSL and achieved remission with the initial dose. However, their average PSL dose remained at 5.5 ± 2.3 mg/day at the end of 1 year. Four RS3PE patients received methotrexate (MTX). Thirteen RS3PE patients use prophylaxes for infection.

3.2. Comparisons of complications occurring before treatment and those occurring 1 year after treatment

Table 1 summarizes the results of the comparison of complications that occurred before the patients’ treatment with corticosteroids. Before treatment, 24 (51.1%) of the RS3PE patients were complicated with HT. Thirteen (27.7%) RS3PE patients developed solid tumors; one had pulmonary cancer, three
had gastric cancers, seven had colon cancers, one had prostatic cancer, one had uterine cancer, and one had ovarian cancer. Eleven (23.4%) RS3PE patients were complicated with DM; IHD and cerebrovascular diseases were complicated in four (8.5%) and three (6.4%) patients, respectively. Three (6.4%) RS3PE patients had dyslipidemia, and one patient had cystitis. There were no significant differences in the prevalence rates of these complications (other than malignancies) between the RS3PE and EORA groups.

During the 1-year follow-up, the number of patients complicated with infections was nine (19.1%) in the RS3PE group, which is a significantly higher incidence compared to the RA patients with infections ($n = 3$, $p = .0485$; Figure 2, Table 2). The infections included pneumonia, pulmonary cryptococcosis, cystitis, oral candida, and varicella zoster of the intercostal nerve region. There were no significant between-group differences in the incidence of the complications HT, DM, dyslipidemia, IHDs, cerebrovascular diseases, and malignancy.

**Table 1.** Clinical characteristics of the RS3PE syndrome patients and elderly-onset RA patients.

|                         | RS3PE syndrome (n = 47) | EORA (n = 46) | p-value |
|-------------------------|-------------------------|---------------|---------|
| Sex, men:women, n       | 28:19                   | 10:36         | <.001   |
| Age at evaluation, y    | 78.4 ± 7.5 (60–89)      | 77.0 ± 6.8 (65–92) | .384    |
| Age at onset, y         | 75.6 ± 7.3 (51–87)      | 75.6 ± 6.4 (65–88) | .060    |
| Disease duration, m     | 2.0 ± 2.2 (0–12)        | 11.1 ± 14.1 (0–60) | <.001   |
| Inflamed joints, n      | 12.3 ± 1.3 (shoulder, 1.6; elbow, 0.9; wrist, 1.4; MCP, 5.5; PIP, 4.5; hip, 0; knee,1.0; ankle, 1.3; MTP, 2.8) | 6.7 ± 1.3 (shoulder, 23; elbow, 12; wrist, 37; MCP, 25; PIP, 31; hip, 4; knee,25; ankle, 14; MTP, 6) | .003 |
| Pitting edema, n        | 47 (right hand, 33; left hand, 33; right foot, 34; left foot, 34) | 3 (right hand, 0; left hand, 0; right foot, 2; left foot, 1) | <.001 |
| WBC, /mm$^3$            | 8,256 ± 2,735 (4,100–15,700) | 7,547.8 ± 2388.7 (4,300–17,700) | .155    |
| ESR, mm/h               | 75.6 ± 35.7 (9–131) (n = 44) | 61.4 ± 29.0 (10–109) | .033    |
| CRP, mg/dL              | 7.6 ± 5.2 (0.43–21.5)   | 2.5 ± 2.7 (0.04–9.83) | <.001   |
| DAS-CRP                 | —                       | 4.3 ± 1.6     | —       |
| RF-positive             | 0 (0.0%)                | 34 (73.9%)    | <.001   |
| ACIA-positive           | 0/32 (0.0%)             | 28/40 (70.0%) | <.001   |
| Initial PSL dose, mg/day, n | 16.5 ± 7.2 (n = 47) | 7.3 ± 4.6 (n = 26) | <.001 |
| Cumulative PSL dose, mg, n | 3201.6 ± 1092.2 (n = 37) | 998.4 ± 1274.1 (n = 46) | <.001 |
| MTX dose, mg/day, n     | 8.5 ± 1.9 (n = 4)       | 7.5 ± 1.7 (n = 27) | .283    |
| Other DMARD use, n      | 0                       | 20 (SASP, 13; BUC, 4; TAC, 8; MZR, 5; IFX, 1; ETN, 7; TCZ, 2; ABT, 3) | <.001 |
| Prophylaxes for infection, n | 13 (INH, 12; ST, 11; Pneumococcus vaccine, 1) | 19 (INH, 15; ST, 3) | .166 |

**Figure 2.** Comparison of complications occurring before treatment and those occurring 1 year after the start of treatment. After the treatment of RS3PE syndrome patients for 1 year, the number of patients complicated with infections increased significantly from one (2.1%) to nine (19.1%).

| Complications                  | RS3PE syndrome | EORA | p-value |
|--------------------------------|----------------|------|---------|
| Hypertension                   | 24 (51.1%)     | 23 (50.0%) | .837   |
| Diabetes mellitus              | 11 (23.4%)     | 10 (21.7%) | .848   |
| Dyslipidemia                   | 3 (6.4%)       | 7 (15.2%) | .198   |
| Ischemic heart diseases        | 4 (8.5%)       | 5 (10.9%) | 1.000  |
| Cerebrovascular diseases       | 3 (6.4%)       | 1 (2.2%) | .617   |
| Infections                     | 1 (2.1%)       | 3 (6.5%) | .355   |
| Malignancies                   | 13 (27.7%)     | 4 (8.7%) | .017   |

ABT: abatacept; ACPA: anti-cyclic citrullinated peptide antibody; BUC: buclamide; CRP: C-reactive protein; DAS-CRP: disease activity score-C-reactive protein; DMARD: disease-modifying anti-rheumatic drug; EORA: elderly-onset rheumatoid arthritis; ESR: erythrocyte sedimentation rate; ETN: etanercept; IFX: infliximab; INH: isoniazid; MCP: metacarpophalangeal joint; MTP: metatarsophalangeal joint; MTX: methotrexate; MZR: mizoribine; PIP: proximal interphalangeal joint; PSL: prednisolone; RF: rheumatoid factor; RS3PE: remitting seronegative symmetrical synovitis with pitting edema; SASP: salazosulfapyridine; ST: trimethoprim-sulfamethoxazole; TAC: tacrolimus; TCZ: tocilizumab; WBC: white blood cell.
3.3. Influence of continuous treatment with PSL on infections

We investigated the factors that contributed to the incidence of infections during the 1-year treatment (Table 3). In the univariate analysis, the p-values for the between-group differences in ESR, CRP, and initial PSL dose were all < 0.05, whereas the p-value for the cumulative PSL dose was not < 0.05. The results of the multivariate analysis demonstrated that the initial PSL dose was the only independent variable associated with the incidence of infections: OR 1.10, 95%CI: 1.01–1.21, p < 0.05.

4. Discussion

To the best of our knowledge, this is the first study to investigate the incidence of complications in patients with RS3PE syndrome, a disease that occurs in the elderly. The average age of the RS3PE patients in this study was 78.4 years. Hypertension complicated the condition of 24 (51.1%) of the RS3PE patients, and DM was present in 11 (23.4%) of the patients. Although the rates of these diseases at entry were relatively high, they were not significantly higher than those of the EORA patients (50.0% and 21.7%). In a study of a Japanese general population >70 years old, the rates of HT patients and DM patients were 73.4% and 22.2%, respectively [4].

Although all of the present patients with RS3PE syndrome responded dramatically well to low-moderate doses of glucocorticoids, they were taking 5.6 ± 2.3 mg/day of PSL even at 1 year after the initiation of the treatment. Before conducting this study we speculated that individuals with RS3PE syndrome might be at an increased risk for CVD; however, CVD was not a common complication in the RS3PE patients. IHDs and cerebrovascular diseases occurred in only four (8.5%) and three (6.4%) of the RS3PE patients, respectively. Even after the corticosteroid therapy, the incidence of IHD and CVD did not increase significantly.

It has been reported that RS3PE syndrome is often complicated with neoplasms [7,8]. In the present investigation, we observed 13 (27.7%) patients complicated with neoplasms before steroid therapy. These patients responded to corticosteroids as well as the patients without neoplasms did. Pulmonary cancer and prostatic cancer developed during the 1-year steroid therapy in one patient each.

We reported that the most common complication in elderly RA patients was infections [9]. It is well

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**Table 2.** Comparison of complications between the RS3PE syndrome and RA groups during the 1-year treatment.

| Complications            | RS3PE syndrome (n = 47) | EORA (n = 46) | p-value |
|--------------------------|-------------------------|---------------|---------|
| HT                       | 2 (4.3%)                | 2 (4.3%)      | .983    |
| DM                       | 2 (4.3%)                | 2 (4.3%)      | .983    |
| Dyslipidemia             | 1 (2.1%)                | 1 (2.2%)      | .988    |
| IHD                      | 1 (2.1%)                | 1 (2.2%)      | .988    |
| CVD                      | 0 (0.0%)                | 0 (0.0%)      | –       |
| Infections               | 1 (2.1%)                | 2 (4.3%)      | .049*   |
| Pneumonia (n = 2)        |                         |               |         |
| Pulmonary cryptococcosis (n = 1) |                   |               |         |
| Cystitis (n = 2)         |                         |               |         |
| Candida (oral cavity) (n = 3) |                     |               |         |
| Herpes zoster (n = 1)    |                         |               |         |
| Malignancies             | 1 (2.1%)                | 2 (4.3%)      | .545    |

*C p < 0.05.

**Table 3.** Factors contributing to the incidence of infections during the patients’ 1-year treatment (univariate analysis and multivariate analysis).

| Parameter                              | Univariate analysis | Multivariate analysis |
|----------------------------------------|---------------------|-----------------------|
|                                       | OR (95%CI)          | p-value               | OR (95%CI)          | p-value               |
| Sex, men:women, n                      | 1.23 (0.28–5.32)    | 0.785                 | 1.13 (0.98-1.31)    | 0.055                 |
| Age at evaluation, y                   | 1.05 (0.94–1.18)    | 0.343                 |                       |                       |
| Age at onset, y                        | 1.06 (0.94–1.20)    | 0.320                 |                       |                       |
| Disease duration, m                    | 0.79 (0.46–1.37)    | 0.326                 |                       |                       |
| Inflamed joint count, n                | 0.94 (0.87–1.02)    | 0.122                 |                       |                       |
| WBC, /mm³                              | 1.00 (0.99–1.00)    | 0.405                 |                       |                       |
| CRP, mg/dL                             | 1.16 (1.00–1.35)    | 0.037                 | 1.21 (0.99–1.50)     | 0.042                 |
| Initial PSL dose, mg/day, n            | 1.12 (1.00–1.26)    | 0.030                 | 1.19 (1.03–1.38)     | 0.007                 |
| Cumulative PSL dose, mg, n             | 1.00 (0.99–1.00)    | 0.709                 |                       |                       |
| Prophylaxes for infections, n          | 4.38 (0.84–22.70)   | 0.079                 |                       |                       |

* p < 0.05.

ACPA: anti-cyclic citrullinated peptide antibody; CRP: C-reactive protein; DAS-CRP: disease activity score-C-reactive protein; DMARD: disease-modifying anti-rheumatic drug; ESR: erythrocyte sedimentation rate; MTX: methotrexate; PSL: prednisolone; RF: rheumatoid factor; WBC: white blood cell.
known that immune function is decreased in the elderly. Aging has been associated with a significant decrease in the number of lymphocytes as well as a decline in acquired immune responses [10]. The production of antibodies against specific extrinsic and intrinsic antigens becomes significantly reduced in aged individuals. In the present patient population, only one patient with RS3PE syndrome was complicated with an infection at entry, but the rate of infections was significantly increased after corticosteroid therapy compared to before the treatment. The infections included opportunistic infections such as candida, varicella zoster, and cryptococcosis.

Corticosteroids were identified in previous studies as a significant risk factor for infections even in patients treated with low-dose corticosteroids (<10 mg/day of PSL) [11–14]. Crowson et al. developed a scoring system to predict the 1-year risk of serious infection in patients with RA [15]. The components of the risk score included age, previous serious infection, and elevated ESR except when due to the use of corticosteroids [16]. The results of our present analyses demonstrated that the patient’s initial PSL dose was an independent variable contributing to infections. High-dose PSL was used in the patients with active RS3PE syndrome, and Candida albicans was the infection that was most frequent complication in the RS3PE group. The Th1 response is protective against Candida, while the Th2 responses are implicated in infection with Candida [17]. The CD4 T-cell-mediated Th2 response might be suppressed by corticosteroids in individuals with RS3PE syndrome.

The response to corticosteroids is quick and dramatic in most cases of RS3PE syndrome. However, the use of corticosteroids should be considered carefully in elderly patients with RS3PE syndrome. Kardes et al. successfully treated two patients with RS3PE syndrome with MTX without adding corticosteroids [18]. Among our patients, four were being treated with MTX with corticosteroids as therapy for RS3PE syndrome, to taper the dose of prednisolone. The efficacy of tocilizumab for RS3PE syndrome that is refractory to corticosteroids was also described [19].

Our study has some limitations. First, we had a small sample size since RS3PE syndrome is not a common disease. A larger number of patients, longer observation period, and a prospective study design are required. The 1-year observation period may be too short to draw any conclusions about CVD complications. Second, we restricted the subjects to patients for whom clinical data were available for 1 year after the initiation of treatment. Ten patients who were not followed for 1 year were excluded from this study. Those who were cured within 1 year were included among these patients.

Our results indicate that infections were significantly increased in elderly patients with RS3PE syndrome during the 1 year after their corticosteroid therapy was begun. The initial dose of corticosteroids was one of the risk factors for infections in these patients. We recommend the use of prophylaxes for patients with RS3PE syndrome while they are being treated with high doses of PSL. In addition, a combination of MTX with PSL may reduce the PSL dose.

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Ethics
This study was performed in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Institutional Review Board of Nagasaki University (approval no. 091126). Written informed consent was obtained from the patients.

Disclosure statement
No potential conflict of interest was reported by the author(s).

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