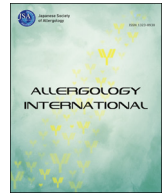Contents lists available at ScienceDirect

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Original Article

Summary of the current status of clinically diagnosed cases of Schnitzler syndrome in Japan

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A R T I C L E   I N F O

A B S T R A C T

Background: Schnitzler syndrome is a rare disorder with chronic urticaria, and there is no report summarizing the current status in Japan.
Methods: A nationwide survey of major dermatology departments in Japan was conducted in 2019. We further performed a systematic search of PubMed and Ichushi-Web, using the keywords "Schnitzler syndrome" and "Japan" then contacted the corresponding authors or physicians for further information.

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Results: Excluding duplicates, a total of 36 clinically diagnosed cases were identified from 1994 through the spring of 2022, with a male to female ratio of 1:1. The median age of onset was 56.5 years. It took 3.3 years from the first symptom, mostly urticaria, to reach the final diagnosis. The current status of 30 cases was ascertained; two patients developed B-cell lymphoma. SchS treatment was generally effective with high doses of corticosteroids, but symptoms sometimes recurred after tapering. Colchicine was administered in 17 cases and was effective in 8, but showed no effect in the others. Tocilizumab, used in six cases, improved laboratory abnormalities and symptoms, but lost its efficacy after several years. Rituximab, used in five cases, was effective in reducing serum IgM levels or lymphoma mass, but not in inflammatory symptoms. Four cases were treated with IL-1 targeting therapy, either anakinra or canakinumab, and achieved complete remission, except one case with diffuse large B-cell lymphoma.
Conclusions: Since Schnitzler syndrome is a rare disease, the continuous collection and long-term follow-up of clinical information is essential for its appropriate treatment and further understanding of its pathophysiology.

Abbreviations

ALP	alkaline phosphatase
CT	computed tomography
CLC	colchicine
CRP	C-reactive protein
CsA	cyclosporine
DFPP	double filtration plasmapheresis
DLBCL	diffuse large B-cell lymphoma
DMARDs	disease-modified anti-rheumatic drugs
ESR	erythrocyte sedimentation rate
KU	Kyoto University
MRI	magnetic resonance imaging
PET	positron emission tomography
PGA	physician global assessment
PSL	prednisolone
PUVA	ultraviolet radiation
RTX	rituximab
SchS	Schnitzler syndrome
SDC	Strasbourg Diagnostic Criteria
WBC	white blood cell
WM	Waldenström macroglobulinemia

Introduction

Schnitzler syndrome (SchS) is a rare disorder characterized by chronic urticarial rash and monoclonal IgM or, rarely, IgG gammopathy. This syndrome was first reported in 1972 by French dermatologist Lilian Schnitzler. Since then, over 200 cases have been reported in 25 countries; most patients were Caucasian.[1,2]

In 2010, Lipsker *et al.*[3] proposed SchS diagnostic criteria. In 2013, Lipsker, Schnitzler, and other experts compiled the current diagnostic criteria (Strasbourg Diagnostic Criteria; SDC),[1] which defined chronic urticarial rash and monoclonal IgM or, rarely, IgG gammopathy as obligate criteria and the following symptoms as minor criteria: recurrent fever, abnormal bone remodeling with or without bone pain, a neutrophilic dermal infiltrate upon skin biopsy, and leukocytosis and/or elevated C-reactive protein (CRP). The major complications are lymphoproliferative disorders,[3] including Waldenström macroglobulinemia (WM), lymphoplasmacytic lymphoma with IgM monoclonal protein.

The first case in Japan was reported in 1995 by Nagoya City University.[4] We recently experienced five cases at Kyoto University (KU),[5] and became aware that there is no established treatment for this syndrome, though some clinical trials have been conducted for anakinra,[6] rilonacept,[7] canakinumab,[8,9] and tocilizumab.[10] To address this situation, we first collected cases of this acquired autoinflammatory disorder in Japan to understand its current status and needs.

Methods

Collecting patient data in Japan

In 2019, Dr. Nobuo Kanazawa conducted a nationwide survey to identify domestic cases of SchS in the dermatology departments of 122 university hospitals and 233 large (more than 500 beds) hospitals. The project was led by Dr. Takashi Hashimoto of the Osaka Metropolitan University and funded by the Science Research Grant for Policy Research on Intractable Diseases from the Ministry of Health, Labor and Welfare, Japan.

Collecting patient data from the literature

Next, we conducted a search of PubMed (National Library of Medicine) and Ichushi-Web (Japan Medical Abstracts Society) using the keywords "Schnitzler syndrome" and "Japan" and collected published manuscripts and conference reports from 1994 to the spring of 2022.

Clinical information collection

From the literature, we extracted the age at onset, symptoms, blood sampling data, imaging data, and treatments performed. We then contacted the authors for more detailed information and a physician global assessment (PGA) for the five primary SchS symptoms (urticarial rash, fatigue, fever/chills, myalgia, and arthralgia/bone pain), which were each graded on a 5-point Likert scale: 0 = no, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe disease activity.[7,8,10] From the authors' responses, we supplemented the existing clinical and laboratory information with the long-term course of treatment and its effects. The study was approved by the ethics committee of KU (R2559).

Results

Patient data collection

The nationwide survey conducted in 2019 identified seven cases (cases 1—6 and 28 in Table 1). We received responses from 109 (31%) of the 355 facilities, including 60 (49%) of the 122 university hospitals and 49 (21%) of the 233 large hospitals. A literature search

Table 1
Demographic and characteristics per the Strasbourg diagnostic criteria.

Case[†]	Age[‡]	M/F	Obligate criteria		Minor criteria				Ref
			Rash[§]	IgM or IgG[¶]	Fever[††]	Bone[‡‡]	Biopsy[§§]	WBC & CRP[¶¶]	
Definitive cases									
1	51	F	+	IgMκ	+	N/A	+	+	11
2	51	F	+	IgMκ	+	N/A	+	+	20
3	45	F	+	IgMκ	+	N/A	+	+	22
4	57	M	+	IgMκ	+	N/A	+	+	23
5	35	M	+	IgMκ	+	N/A	+	+	N/A
6	40	F	+	IgM	+	N/A	+	+	24
7	75	F	+	IgMκ	+	N/A	N/A	+	13
8	46	M	+	IgMκ	+	+	N/A	N/A	16
9	39	M	+	IgMκ	+	N/A	+	+	17
10	68	F	+	IgMκ	+	N/A	+	−	18
11	42	F	+	IgMκ	+	N/A	+	+	4
12[†]	76	M	+	IgMκ	+	N/A	+	+	25
13	73	M	+	IgMκ	+	−	+	+	27
14	62	F	+	IgMκ	+	N/A	+	+	28
15[†]	71	F	+	IgMκ	+	N/A	+	−	29
16	72	M	+	IgM	+	+	+	N/A	30
17[†]	63	F	+	IgM	+	N/A	+	N/A	32
18	64	M	+	IgM	+	N/A	+	+	33
19	63	F	+	IgM	+	N/A	+	−	35
20	45	M	+	IgMκ	+	+	+	+	36
21	61	F	+	IgMκ	+	−	+	+	5,56
22	60	M	+	IgMλ	+	N/A	+	+	5,39
23	43	F	+	IgMκ	+	+	+	+	5
24	56	F	+	IgMκ	+	+	+	+	5
25	41	M	+	IgMκ	+	N/A	+	+	38
26	54	M	+	IgMκ and IgGκ	+	N/A	−	+	40
27	49	M	+	IgMκ	+	N/A	−	+	N/A
Probable cases									
28	67	F	+	IgMκ	−	N/A	+	−	21
29	75	M	+	IgMκ	−	N/A	+	−	12
30	68	M	+	IgGκ	+	N/A	+	N/A	14
31	62	M	+	IgMκ	+	N/A	N/A	−	15
32	65	M	+	IgMκ	+	N/A	N/A	N/A	26
33	57	F	+	IgM	−	N/A	+	N/A	34
34	65	M	+	IgMκ	−	N/A	N/A	+	37
Unmet Cases									
35	39	F	+	−	+	+	+	+	19
36	42	F	+	IgAλ	+	−	N/A	+	31

N/A, Not performed or not mentioned in the literature.

  [†] Case with: Indicates that the patient is already dead.

  [‡] Age = the age (year) of onset.

  [§] Rash = urticarial rash.

  [¶] IgM or IgG = the monoclonal IgM or IgG and subtype of κ or λ, where available.

  [††] Fever = recurrent fever over 38 °C, and otherwise unexplained.

  [‡‡] Bone = the presence or absence of abnormal bone remodeling with or without bone pain as assessed by bone scintigraphy, MRI, or elevated bone alkaline phosphatase.

  [§§] Biopsy = the presence or absence of neutrophilic dermal infiltrate without fibrinoid necrosis and significant dermal edema in the biopsy specimen.

  [¶¶] WBC & CRP = the presence or absence of leukocytosis (neutrophils >10,000/mm³) and/or elevated CRP (>30 mg/L).

revealed 10 cases published in English,[4,11–19] 21 cases published or presented in Japanese,[20–40] and our previous 5 cases at KU Hospital.[5] Excluding duplicates, a total of 36 clinically diagnosed cases were identified in Japan from 1994 to the spring of 2022, of which 27 were definitive cases when checked with the SDC, 7 were probable, and 2 did not meet the SDC (Table 1). An additional case was reported as SchS,[41] but we excluded it since the reporters themselves revised the diagnosis to polyarteritis nodosa with secondary amyloidosis.

Epidemiology

The mean age of onset for the 27 definitive cases is 55.6 years, with a male-to-female ratio of about 1:1. Among the 36 total cases, the mean age of onset is 56.5 years, and the gender composition remained the same. On average, based on available data for 35 patients, it took 3.3 years from the first symptom, mostly urticaria, to reach a final diagnosis of SchS. None of the cases presented with a family history of SchS symptoms nor was there any identifiable, common patient history.

Among the 36 cases, we were able to contact the paper authors or the patients' physicians for 30 cases; three definitive cases were reported to have died (Table 1). Two cases of SchS-related lymphomas were reported: a mature B-cell lymphoma of uncertain histologic subtype from a probable case[18] and a diffuse large B-cell lymphoma (DLBCL) from a definitive case.[32] The former survived following treatment, but the latter patient died; an autopsy revealed that the intima of the great vessels and heart valves were covered with IgM-positive deposits. The remaining two definitive patients died of diseases unrelated to SchS, interstitial pneumonia[25] and non-occlusive mesenteric ischemia.[29] Eight cases (cases 5, 7, 10, 11, 13, 18, 31 and 33) have not recently followed up with their physicians. However, 19 patients are still attending their care physicians, 7 of whom (cases 1, 2, 6, 9, 14, 21 and 24) are alive more than 10 years after the symptom onset, and all are definitive cases. The mean follow-up period was 6.1 years.

Obligate criteria

All 36 patients had a chronic urticarial rash (Fig. 1A, Supplementary Fig. 1A), an obligate criterion of the SDC.[1] The frequency of urticaria ranged from daily to several times a year, and the extent of skin lesions varied over the trunk and extremities, sparing the head, palms, and soles. Usually, the lesions were non-pruritic and lasted more than 24 h.

Gammopathy was present in all, except one unmet case[19] for the SDC, and 34 cases were monoclonal. One patient presented with IgGκ and IgMκ biclonal gammopathy[40] (Fig. 1B, C), and we counted this case as definitive. Among the 27 definitive cases, there was no mention of the light chain subtype for 5 patients but all patients, except the biclonal gammopathy case, had monoclonal IgM gammopathy, 20 (74%) had the IgMκ subtype, and 1 (3.7%) IgMλ.[5] In contrast, one probable case of IgGκ subtype[14] and an IgAλ subtype unmet case[31] were reported (Supplementary Fig. 1C). Based on the available data from 27 definitive patients, the average IgM serum level at first visit was 792.4 mg/dl (normal range; male: 33–190 mg/dl, female: 46–260 mg/dl) (Fig. 2A, B). Even in definitive cases, there were cases with IgM levels close to the upper limit of normal in both men and women (Fig. 2A, B), but over time, many cases were observed to have elevated IgM levels (Fig. 2C). The outliers (*1 in Fig. 2A and *2 in 2B) are cases 9[17] and 19,[35] respectively; case 9 presented 10 years after the onset of urticaria; detailed information for case 19 was unavailable. Bence-Jones proteins in the urine were only mentioned for 11 cases of SchS, out of which 6 definitive cases (cases 2, 9, 11, 12, 14 and 22) and one probable case (case 30) were positive.

Minor criteria

One of the minor SchS criteria was fever. In definitive cases, all patients had recurrent fevers (Fig. 1D), mostly up to 38–39 °C, sometimes accompanied by a rash. Febrile events ranged in frequency from daily to several times per year. On the other hand, among the 36 cases for which information could be collected, 4 probable cases did not develop fever (Supplementary Fig. 1D).

In Japan, magnetic resonance imaging (MRI) and bone scintigraphy were not performed routinely but occasionally, when bone pain or arthralgia was observed. Only 9 patients were examined using these techniques, and 5 definitive cases[5,16,30,36,39] and one
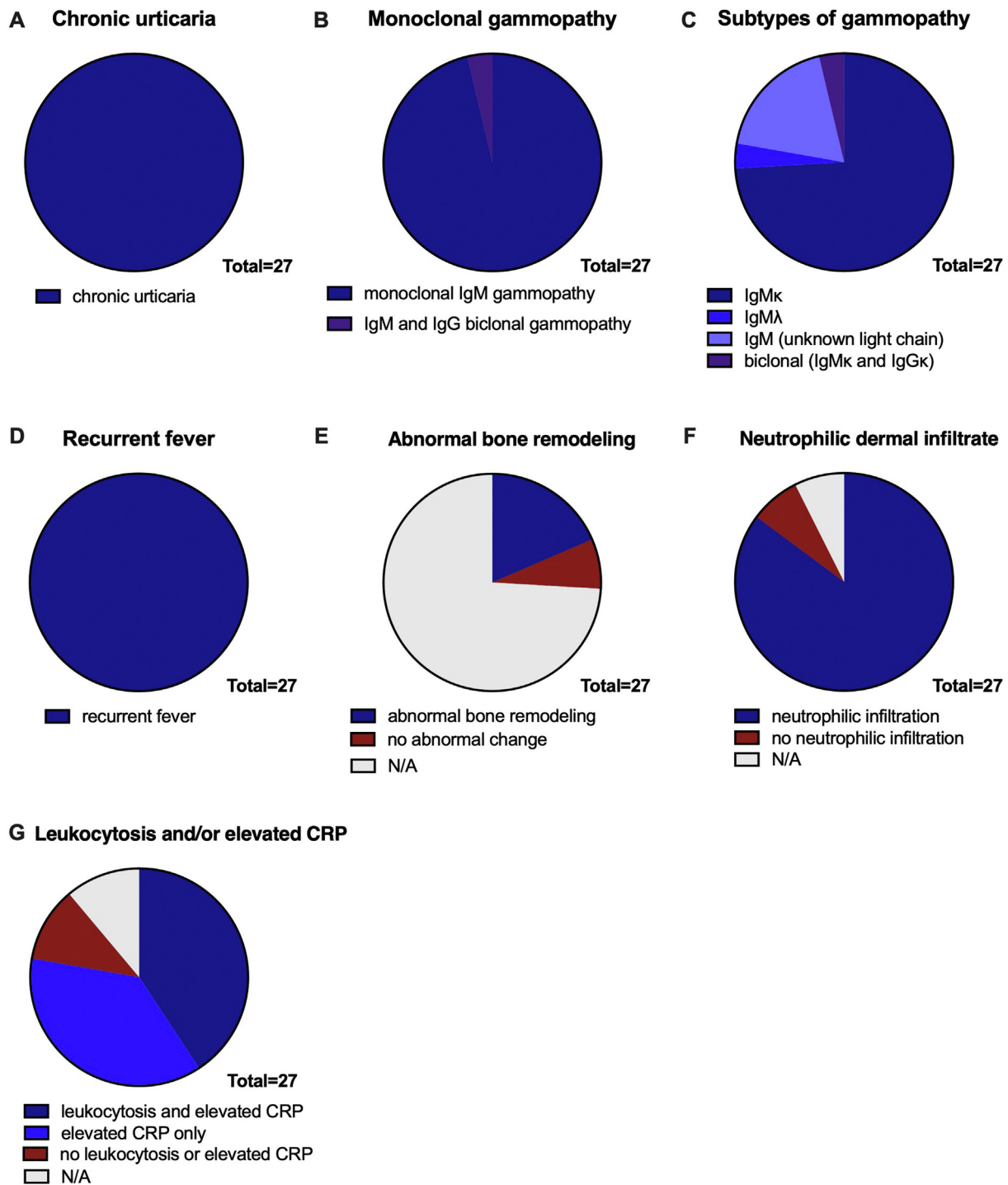
Fig. 1. The ratio of definitve patients with clinical and laboratory features defined in the Strasbourg diagnostic criteria (n = 27). **(A)** Chronic urticaria was seen in 100% of patients. **(B)** Monoclonal IgM or IgG gammopathy was seen in 100% of patients. **(C)** Subtypes of monoclonal gammopathy. **(D)** Recurrent fever was seen in 100% of patients. **(E)** Five cases were positive for abnormal bone remodeling (n = 7). **(F)** Skin biopsy revealed 23 cases with neutrophilic dermal infiltrate (n = 25). **(G)** Leukocytosis and/or elevated CRP was seen in 21 cases (11 with both leukocytosis and elevated CRP, and 10 with elevated CRP only); 3 cases had neither leukocytosis nor elevated CRP.

unmet case[19] were positive for abnormal bone remodeling of the lumbar vertebrae, femur, or tibia (Fig. 1E, Supplementary Fig. 1E). In some cases, positron emission tomography (PET)/computed to-mography (CT) revealed fluorodeoxyglucose uptake by the bone marrow,[19,31] or osteosclerosis was discovered by a whole-body CT scan[5] or X-ray.[37] Out of 36 patients, bone pain, mostly of the femur or tibia,[5,17,39] affected 8 out of 27 definitive cases, and 2 probable and one unmet cases, while 10 out of 27 definitive cases, 3 probable

and one unmet cases suffered from joint pain, such as in the knees.[12,14,18]

Skin biopsies were performed in 25 definitive cases, and 23 showed perivascular and/or interstitial infiltrate of neutrophils (Fig. 1F), sometimes with lymphocyte or eosinophil infiltration and nuclear dust. Among probable and unmet cases, all the 5 cases (4 probable and one unmet) in which skin biopsy was performed showed neutrophilic infiltration, and one of the probable cases
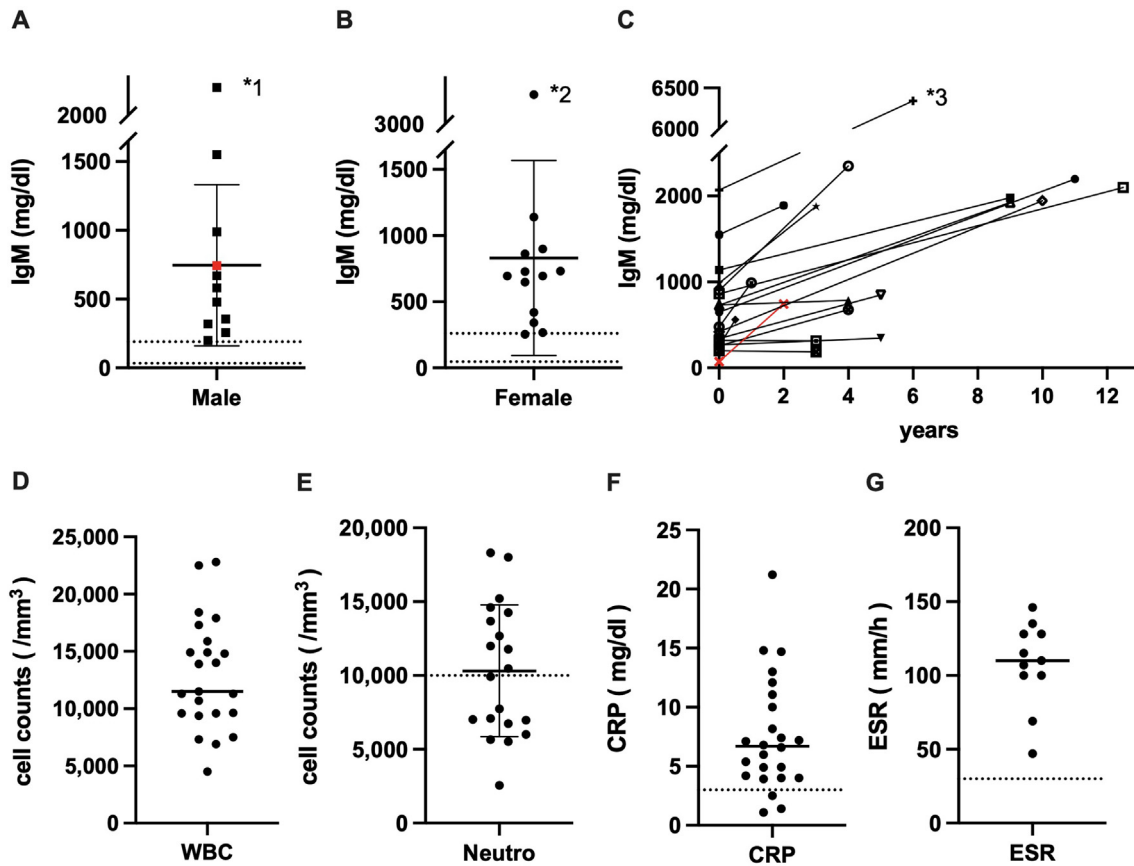
Fig. 2. Laboratory data of definitive patients. **(A, B)** Serum IgM levels at first presentation of male (n = 11) and female (n = 13) patients. The standard value (male: 33–190 mg/dl, female: 46–260 mg/dl) is marked with a dotted line. **(C)** The long-term changes of serum IgM levels (n = 18). In case 12 (red line), the serum IgM level was 71 mg/dl when the patient first noticed urticaria and fever and visited the previous doctor, but at the first presentation to the authors it had risen to 743 mg/dl,[25] which was plotted in **(A)** (red dot). **(D)** White blood cell counts at first presentation (n = 23). **(E)** Neutrophil counts at first presentation (n = 20). The threshold in the Strasbourg diagnostic criteria (neutrophils >10,000/mm^3) is marked with a dotted line. **(F)** Serum CRP levels at first presentation (n = 24). The threshold in the Strasbourg diagnostic criteria (CRP >3.0 mg/dl) is marked with a dotted line. **(G)** ESR levels at first presentation (n = 10). The threshold described as biological findings of SchS patients by Simon et al.[1] (>30 mm/h) is marked with a dotted line.

showed basophilic infiltration.[12] No fibrinoid necrosis of the vessel wall was reported. Immuno-deposits consisting of IgM, C3, and sometimes IgG were seen in a few cases,[4,18,29] but the deposit locations varied from interstitial granular patterns to along vessel walls.

In 27 definitive cases, leukocytosis (neutrophils >10,000/mm^3) and/or elevated C-reactive protein (CRP >3 mg/dl) were observed in 21 cases (Fig. 1G); 11 of these presented with leukocytosis (average = 10,311/mm^3) and all 21 presented with elevated CRP (average = 7.6 mg/dl) (Fig. 2E, F). Erythrocyte sedimentation rate (ESR), another laboratory marker of systemic inflammation, was elevated in most patients (when tested, 10 of 27) for an average of 107 mm/h (Fig. 2G). When probable and unmet cases were included in the analysis, 24 of the 30 cases with data were found to have leukocytosis and/or elevated CRP (Supplementary Fig. 1G), including 12 cases with leukocytosis (average = 10,090/mm3) but all 24 cases had elevated CRP (average = 7.2 mg/dl) (Supplementary Fig. 2E, F). ESR was elevated in 12 of 36 tested for an average of 108 mm/h (Supplementary Fig. 2G).

Other features

Some cases of SchS progress to hematologic tumors,[2] and this evaluation is necessary. Lymphadenopathy was reported in 5 definitive patients (cases 8, 13, 14, 16 and 20)[16,27,28,30,36] and each one probable (case 34)[37] and unmet case (case 36).[31] Only two definitive patients[16,30] had hepatosplenomegaly. Bone-marrow aspiration was performed in 19 cases, and normal bone marrow was observed in most cases, but one each of definitive (case 2), probable (case 30), and unmet (case 36) cases showed a moderate increase in plasma cells without atypical differentiation. Only in a definitive case 10,[18] which had B-cell lymphoma, did the analysis of bone-marrow aspirates indicate the existence of clonal, mature lymphoma cells.

One definitive patient (case 15)[29] developed membranoproliferative glomerulonephritis due to cryoglobulinemic vasculitis. None were found to develop amyloidosis.

Genetic analysis

Previously, somatic mosaicism of *NLRP3* in the myeloid lineage and the *MYD88* p.L265P mutation were found in a few cases of SchS[42,43]; a gain-of function mutation in *NLRP3* causes overexpression of IL-1β in cryopyrin-associated periodic syndrome (CAPS),[44] and the *MYD88* p.L265P mutation is detectable in more than 90% of WM.[45] In the survey of Japanese hospitals, only a few patients were screened for these mutations, but none presented with either an *NLRP3* or *MYD88* mutation. The somatic mosaicism of *NLRP3*, first detected in CAPS by our group,[44] was not reported either.

Treatment

Supplementary Table 1 shows treatments performed on each case. Since the treatment effects described in the literature for SchS
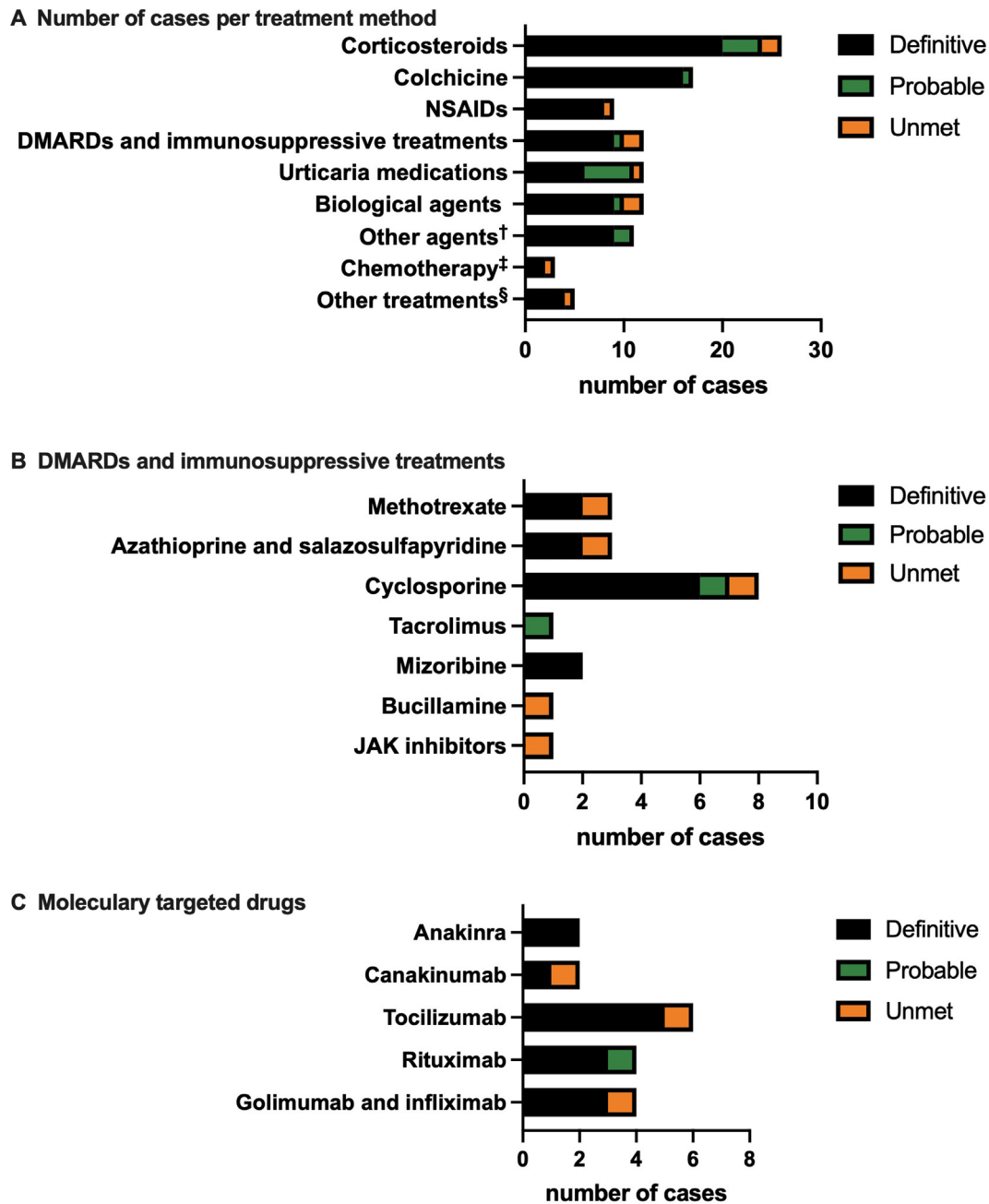
Fig. 3. Number of cases treated with each treatment method. **(A)** is a summary, while **(B)** or **(C)** is more detailed data. **(B)** Number of patients treated with DMARDs, immuno-suppressive agents and biological agents. **(C)** Number of cases treated with molecularly targeted drugs including IL-1 blocking therapies (Anakinra and Canakinumab), an anti-IL-6 agent, Tocilizumab, and an anti-CD20 antibody, Rituximab. Other agents[†]: KI (potassium iodide), DDS (diaminodiphenyl sulfone), RXM (roxithromaycin), and BP (bisphosphonate). Chemotherapy[‡]: R-EPOCH (rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin), DMVM-IFNa (dexamethasone, ranimustine, vincristine, melphalan, and interferon-α), and BD (bortezomib and dexamethasone). Other treatments[§]: Radiation, PUVA (psoralen and long-wave ultraviolet radiation), DFFP (double filtration plasma-pheresis), and TKR (total knee replacement).

are short-term and lack standard evaluation criteria, we evaluated the disease status of the 19 cases for whom we had direct contact with their physicians using the provided PGA scores (Supplementary Table 2). Of these, 16 had a definitive diagnosis, one had a probable, and two did not meet SDC.

Corticosteroids were the most common treatment; used in 20 definitive, 4 probable and 2 unmet cases (Fig. 3A, Supplementary Table 1). They were usually started at high doses (over 0.5 mg/kg/day) and were effective. However, the side effects of corticosteroids limit its use at high doses for extended periods, and symptoms sometimes recurred when corticosteroids were tapered off.

Therefore, most cases were treated with other therapies in addition to steroids, with the exception of a definitive case 14,[28] who was maintained only on prednisolone (PSL) 15 mg/day (Supplementary Table 2).

Colchicine (CLC) was used in 16 definitive and one probable cases (Fig. 3A). Among 19 cases under follow-up (Supplementary Table 2), CLC was administered to 9 definitive cases, and 4 of the 9 patients achieved a PGA of zero. Three of these patients (cases 1, 2 and 5) were treated with CLC alone and one (case 4) with CLC plus 2 mg/day PSL. In three cases (cases 6, 12 and 27), the post-treatment PGA score improved, but did not reach zero. Two cases (cases 3 and

25) showed no clinical response to treatment with CLC. Among eight cases where information could not be confirmed directly with the care physicians and was collected only from the literature, two (cases 7 and 29) reportedly showed improvement following CLC therapy. Briefly, for a probable case 29,[12] who was resistant to antihistamines and omalizumab, and a definitive case 7,[13] who responded to 30 mg PSL but relapsed upon tapering, the initiation or addition of CLC dramatically improved symptoms. The remaining six cases[4,5,17,33] showed little or no response to CLC.

Both in the literature and follow-up data, NSAIDs alone had little therapeutic effect but reduced fever and bone pain when used on demand (Supplementary Table 2).[4] According to the literature we collected, most kinds of disease-modified anti-rheumatic drugs (DMARDs) and immunosuppressive treatments (Fig. 3B) like azathioprine, methotrexate, mizoribine, salazosulfapyridine, and tacrolimus were ineffective,[4,5] while cyclosporine (CsA) was sometimes effective but difficult to continue due to side effect.[11] Common urticaria medications, like antihistamines and omalizumab, were ineffective therapies for SchS.[12,19,21]

Molecularly targeted drugs (Fig. 3C) were also used. IL-1 blocking therapy is regarded as one of the most effective treatments[2] but was tried only in a few cases in Japan. Anakinra, an IL-1 receptor antagonist, was used in two definitive cases,[5,32] one of whom died of DLBCL (case 17). Canakinumab, an anti-IL-1β antibody, was used in two cases, one is definitive and the other is unmet case who does not have monoclonal IgM.[5,19] In the three cases under follow up that received either of the IL-1-targeting therapies, a PGA of zero was achieved, but serum IgM levels in two definitive cases did not improve (Supplementary Table 2).

Tocilizumab, an anti-IL-6 agent, was used in six cases (Fig. 3C). The literature showed that initiating tocilizumab dramatically improved laboratory abnormalities, joint symptoms, and fever.[5,30,39] Two definitive patients (cases 22 and 26) have been on tocilizumab for 1 and 3 years, respectively, and both have achieved a PGA of zero (Supplementary Table 2). However, some patients treated with tocilizumab experienced symptom recurrence within a few years (definitive cases 21, 23, and unmet case 36).

The anti-CD-20 antibody rituximab (RTX) was used in five cases (Fig. 3C). RTX was effective in improving serum IgM levels or lymphoma lesions, but was insufficient for cutaneous symptoms.[18,33] According to follow-up data for a probable case 28, after receiving five doses of RTX, the patient remained asymptomatic for 2 years with PSL, CsA, and diaminodiphenyl sulfone; however, the withdrawal of CsA was accompanied by an urticarial rash. In a definitive case 9, an interview revealed that after their serum IgM level rose to 6342 mg/dl (*3, Fig. 2C), seven RTX injections lowered serum IgM, but they gradually relapsed with fevers and high CRP. In another definitive case 10, where a retroperitoneal tumor suggested to be a B-cell lymphoma was found,[18] the mass disappeared with RTX therapy but the urticarial rash was resistant. The rash gradually improved with post-RTX radiation along with complete remission of the mass.

Chemotherapy regimens for malignant myeloma were performed in three cases (Supplementary Table 1); one definitive case combined with RTX failed against DLBCL,[32] one unmet case achieved a reduction of paraprotein but failed at improving symptoms,[31] and another definitive case was repeated three times before reducing paraprotein levels but still failed to control skin eruptions.[36]

Psoralen and long-wave ultraviolet radiation (PUVA) was tried in one case,[27] and while symptoms improved, it needed to be repeated. In cases 15 and 20,[29,36] double filtration plasmapheresis (DFPP) temporarily improved serum IgM levels and skin symptoms but they relapsed after discontinuation (Fig. 3A).

Discussion

In this survey, 36 clinically diagnosed cases of SchS were identified, which we believe includes all the cases diagnosed in Japan, of which 27 were definitive cases when checked for SDC, 7 were probable, and 2 did not meet the SDC (Table 1). We also followed up with the reporting author and/or physician. Since this disease is rare, with a total of only about 300 cases reported worldwide to date, mainly in Europe and the United States,[2] it is essential to first determine the number of cases, the clinical course and treatment course, also in Asian country, Japan. We believe that this report will raise awareness of potential and under-diagnosed patients.

The mean age of onset and clinical characteristics of the Japanese cases are similar to previous reviews from overseas,[2] except that objective findings of abnormal bone remodeling, arthralgia, bone pain, and/or anemia are less common in Japanese cases (Fig. 1E); comparing 27 definitive cases in this Japanese research with 281 cases in the previous review,[2] abnormal bone remodeling in only 5 out of 9 tested cases vs 85% (82 out of 97 tested cases showed increased uptake by bone scintigraphy), arthralgia in 37% vs 68% (192 out of 281 cases), bone pain in 29.6% vs 55% (155 out of 281 cases), and anemia 0% vs 63% (62 out of 98 cases), respectively. One reason is that SchS is described as an urticaria-related disease in the Japanese urticaria practice guidelines and is highly recognized by dermatologists in Japan. It may be necessary to raise awareness that abnormal bone remodeling is better detected by MRI or bone scintigraphy than PET/CT.[46] Since few patients reported bone pain or arthralgia and a very few cases showed elevated alkaline phosphatase (ALP), it is possible that the number of cases with abnormal bone remodeling is really small in Japan, rather than it being overlooked.

Of note, chronic urticaria often precedes other symptoms, and it may take several years to complete the symptoms. In particular, paraprotein and hyper IgMemia may not present in the first 2—3 years.[25] Some patients had serum IgM levels near the upper border of normal at their first visit (Fig. 2A, B), and IgM levels gradually increased over the course of the disease (Fig. 2C). Therefore, it is necessary to monitor immunoglobulins continuously if SchS is suspected. In fact, even in a definitive case 12,[25] the serum IgM level was 71 mg/dl when the patient first sought care for urticaria and fever, but 2 years later it had risen to 743 mg/dl (red dot, Fig. 2A) when he presented to the authors and was diagnosed with SchS. Similarly, low inflammatory markers at first visits (Fig. 2D, E) do not rule out SchS, and must be reexamined especially when a patient is symptomatic.

Regarding treatment, Japan seems to be unique in that CLC is used more (17/36) than in other countries (51/281),[2] possibly due to difficulty accessing IL-1-targeting therapy. CLC inhibits the formation of NLRP3 inflammasomes by disrupting microtubules, which decreases IL-1β production,[47] and inhibits neutrophil recruitment.[48] Cases 1, 2, and 4 were initially treated with either PSL or CsA, which were successfully tapered off after the addition of CLC. Case 5 has been successfully treated with CLC only since his SchS diagnosis, while case 25 was initially treated unsuccessfully with CsA and high-dose of PSL and switched to CLC, but was still resistant to CLC. Though the number of cases is low for generalizable conclusions, those who respond well to low-dose PSL or CsA are likely to have their symptoms controlled with CLC. Simon et al.[1] recommended that cases without severe symptoms or persistent, elevated inflammation markers should be controlled with CLC.

Patients with severe symptoms may initially respond well to tocilizumab but might develop secondary failure. In addition, in most cases treated with IL-1 targeting therapy, the paraprotein levels increased progressively even when autoinflammatory

symptoms were well-controlled.[5] A similar phenomenon was observed in the long term study of canakinumab on SchS,[8] which suggests that suppressing autoinflammation may not prevent lymphoma development. In our present survey, the detailed clinical course is unknown outside of a postmortem report, but it was reported that anakinra did not prevent the development of DLBCL in case 17.[32] In contrast, only RTX succeeded in lowering serum IgM levels. Since erythema and fever remained or recurred in all RTX-treated patients, we suspect that immune cells such as neutrophils and mature plasma cells that do not express CD20 are responsible for the inflammation. Recently, Masson Regnault et al. reported that the spontaneous release of proinflammatory cytokines by the peripheral blood mononuclear cells of SchS patients was higher than in controls, suggesting myeloid inflammation in SchS.[49]

Thus, the most interesting part of SchS is the association between the pathogenesis of autoinflammatory symptoms and monoclonal IgM gammopathy. One of the reasons why SchS is considered an acquired autoinflammatory syndrome is that it shares clinical manifestations with CAPS, in which mutations in *NLRP3* cause clinical symptoms such as urticaria, fever, and abnormal bone remodeling. NLRP3 is an intracellular pattern recognition receptor, and activation of this molecule leads to the formation of inflammasomes and activation of IL-1β, one of the cytokines that trigger inflammation.[50,51] Therefore, acute-phase inflammatory findings observed in CAPS, such as clinical symptoms and abnormal laboratory values, are clearly mediated by IL-1β. Nevertheless, Louvrier et al. recently reported that no somatic or germline pathogenic variations have been identified in *NLRP3* in their large cohort of 40 SchS patients,[52] indicating that *NLRP3* is not a potential candidate gene for SchS and that previously reported SchS patients with an *NLRP3* mosaic mutation may instead have a late-onset NLRP3-autoinflammatory disease.[53] However, the efficacy of IL-1 targeting therapy for SchS probably indicates that IL-1β is the main actor of SchS inflammation, and thus, if accessible, SchS should be treated with IL-1 targeting therapy, as the therapeutic effect on inflammation lasts for a long observation period. Since there is no difference in the clinical presentation except for fewer findings associated with abnormal bone remodeling than in foreign patients, we expect that IL-1 targeted therapy will be successful in Japanese patients with SchS. When the therapy is introduced in Japan, further observation is needed to determine whether long-term treatments targeting IL-1 can prevent IgM elevation and progression to hematologic malignancies.

Conversely, MYD88, of which gain-of-function mutations were reported in more than 90% of WM,[45] is involved in signal transduction downstream of the IL-1 receptor. Neutrophil infiltration of the skin, which causes an urticaria-like rash, and abnormal bone remodeling in SchS, can be evoked by enhanced IL-1R1/MYD88 signaling.[54,55] Although the mechanism of SchS development remains unclear, we believe that accumulating detailed clinical manifestations is a reliable approach to elucidating its pathogenesis.

In summary, all Japanese cases clinically diagnosed as definitive SchS showed urticarial rash, monoclonal IgM gammopathy and recurrent fever. Most of their clinical features are similar to that of foreign cases, but less showed abnormal bone remodeling and more cases were treated with Colchicine than foreign cases. In contrast, this study has limitations. Although this research covers almost all the SchS cases diagnosed in Japan, statistical analysis was impractical due to the number of cases and the lack of unified treatment plan.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2022.11.004.

Authors' contributions

RT-I, NaK, ToK, TaN, KI, TJ, HY, YuT, NoK and KeK designed the study and wrote the manuscript. YK, MY, KN, OT, YY, KaK, YM, YoT, MihH, TakuK, ST, TakaK, YF, KM, TF, TA, TM, ToN, MK, HK, YO, AM, MicH, TS, and AA contributed to data collection. HA performed the statistical analysis. All authors read and approved the final manuscript.

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